THE SKIN REACTIONS, BLOOD CHEMISTRY AND PHYSICAL STATUS OF "NORMAL" MEN AND OF CLINICAL PATIENTS

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The Skin Reactions, Blood Chemistry and Physical Status of "Normal" Men and of Clinical Patients

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We are under obligation to the following collaborators:

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ADOLPH HARTUNG, M.D., Professor of Roentgenology, University of Illinois (examination of all roentgenograms)

MICHAEL GOLDENBURG, M.D., Surgeon, Illinois Charitable Eye and Ear Infirmary (examination and reference of all patients with glaucoma)

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In the technical and statistical work we gratefully acknowledge the assistance of the late Serguis Arquin, M.D., George E. DeTrana, M.D., John G. Hillebrand, M.D., George Milles, M.D., Knute Reuterskiold, M.D., William Boikan, M.D., Louis A. Richburg, M.D., Louis Parmacek, M.D., and Miss Mildred Rosenberg.

Mrs. Helen Kahn, Serologist, Research and Educational Hospital, carried out the Wassermann Tests; R. G. McFate, M.S., Chemist, Research and Educational Hospital, the cholesterol determinations.

Financial support was accorded us from the funds of the Graduate School of the University of Illinois.

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548
1930

CONTENTS

PAGE

I. General Correlations in One Hundred So-Called Normal Men..... 5

II. The Clinical Status of the Group of One Hundred "Normal" Men.... 37

III. Detailed Study of the "Normal" Group and of Miscellaneous Clinical Patients 52
- Method of Presentation of Results..... 52
- Blister Time 52
- Capillary Permeability 59
- Inflammatory Index 62
- Calcium, Potassium and K/Ca Ratio..... 66
- Total Proteins 80
- Globulins 82
- Kromayer Erythema Time..... 85
- Basal Metabolic Rate..... 87
- Resistance of the Skin to Electric Current..... 91
- Muscle Reactivity 94
- Reaction of Pulse Pressure to Epinephrine..... 97
- CO_2 Combining Power..... 101
- Ice Reaction Time..... 103
- Weight/Length Ratios 106
- Cholesterol 110
- Reactivity to Epinephrine: The Wheal..... 112
- Reactivity to Epinephrine: The Flare..... 115
- Reactivity to Thyroxin: The Wheal..... 118
- Reactivity to Thyroxin: The Flare..... 120

IV. The Relation of the Reaction to Epinephrine to the Potassium/Calcium Ratio and to Other Ratios. Clinical Response to Tests..... 121

V. The Patient with Exophthalmos and the Nervous Patient..... 135

VI. Patients with Glaucoma and Their Vascular Reactions..... 150

VII. Sensitized Persons and Persons with Diseases of the Skin..... 156

VIII. A Study of Eighty-Three Tuberculous Patients..... 163
- A. General Correlations 163
- B. Detailed Study of the Reactions of Persons with Tuberculosis.. 182
- C. Clinical Study of Alterations in the Permeability of the Capillaries in Patients with Tuberculosis..... 236
- D. A Study of the Reaction to Epinephrine in Tuberculous Patients 260
- E. Composite Curves of Cardiovascular Reactions Following Injections of Epinephrine in Tuberculous Patients..... 269
- F. The Leukocytic Reaction of the Tuberculous Patient Following the Intracutaneous Injection of Aolan..... 272

IX. The Intracutaneous Reactions to Injection of Pharmacologic Substances During Chill and Fever..... 276

X. Discussion and Deduction..... 278

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I. GENERAL CORRELATIONS IN ONE HUNDRED SO-CALLED NORMAL MEN*

The studies in which one of us (W. F. P.) has been interested during the past five years had their inception in the problems of nonspecific resistance to disease. Closely associated has been a consideration both of allergy and of autonomic derangement, during the course of which individuals react in an abnormal manner to a nonspecific stimulus.

The clinical picture of disease is obviously the reaction of the individual organ or the organism as a whole to an insult. Normally, the insult provokes stimulation, made manifest in various ways, but cellular inhibition, fatigue, paralysis and death may all play a part simultaneously in the sum total of this clinical picture. Not only does the insult vary qualitatively as it may quantitatively, but the individual response will be modified because of inherent differences in the inherited germ plasm, because of differences in the relative activity or inactivity of the glands of internal secretion, because of diet, age, fatigue, previous experience (sensitization or immunity), preexisting or concomitant disease, psychic states, climate, temperature, etc.

It is a subject that does not lend itself readily to study because the degrees of reactivity of the different tissues of the body which we commonly use for examination (skin, nervous tissues, mesenchyme [bone-marrow, leukocytes, endothelium, etc.]) are not necessarily coordinate. Certainly, the reactivity of the epithelium may not correspond with that of the smooth musculature of the blood vessels, and the smooth musculature of the blood vessels may give no index of the status of the capillary endothelium. Recent investigations of the autonomic responses of the body have made this clear.

In its broader aspects, such a study deals with individual constitutional reactivity. But we have felt that in seeking to define constitution in terms of measurable biologic reactions rather than in developmental attributes, some progress might be achieved. The clinician speaks of "lowered resistance" or "good resistance." Generally that is an estimate based on the appearance of the patient, the color and the texture of the skin, the muscular development, the posture and the tonus, the appearance of the fat depots and of the mucous membranes and the mental attitude—the many subtle differences in the physical appearance of the patient. In making his general estimate, the physician usually fuses both constitutional factors and the factors that are the result of environmental forces (condition).

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* From the Department of Pathology of the University of Illinois College of Medicine.

To Eppinger and Hess [1] we owe the introduction of one of the first of the modern methods useful in the estimation of individual reactivity, namely, the injection of epinephrine hydrochloride. Eppinger and Hess classified their patients as sympatheticotonic or vagotonic. Clinical experience, however, has clearly demonstrated that this sharp division is not tenable; that there are many gradients. In addition, it is known that the relative reactivity of the smooth musculature of the blood vessels is by no means a criterion of the relative reactivity of other tissues.

Such studies of the reactivity of the patient are by no means of purely theoretical interest. It is true that the subject of inflammation per se, having progressed through cycles of interpretation from the periods purely speculative to the period of intensive objective research, from which it is just emerging, seems, perhaps because of the very mass of accumulated information, now in danger of being submerged in metaphysical abstractions or a one-sided insistence on relatively unimportant detail. This is unfortunate, because inflammation should be a subject for clinical, never philosophic, study.

Partly, the difficulty is to be sought in the fact that the purely histologic concept of pathology is no longer adequate to the pace of the correlated sciences. Pathology is stepping from cellular to molecular changes and histology must make ever greater use of chemical and physical tools. Partly, the reason is to be sought in the definite realization of an all-embracing interrelation and integration of cell and organ functions that make up the totality of the person. While, therefore, the interests of investigators must center on ever smaller objects as they approach molecular pathology, these interests must, at the same time, become wider as they include constitutional pathology, the study of the functional reactions of the entire organism. It is no longer possible to expect a satisfying solution of problems unless the range of the inquiry is so extended.

Schade [2] led the way in bringing together much of the pioneer work that underlies molecular pathology. The entire range of subjects grouped together as pathologic physiology forms the real background. Particularly, the chemical correlations of the Kraus school,[3] in which the effort has been made to associate every-day medical problems with the chemical status of the individual person, seem to us to have been of greatest value. They took origin in earlier work of American physiologists. When one turns to problems of constitution,

1. Eppinger, H., and Hess, L.: Ztschr. f. klin. Med. **68**:205 and 230, 1909.

2. Schade, H.: Physikalische Chemie in der innere Medicin, ed. 3, Dresden, Theodor Steinkopff, 1923.

3. Kraus, F.: Allgemeine und spezielle Pathologie der Person: I. Tiefenperson, Leipzig, Georg Thieme, 1926.

it is particularly Bauer [4] who has emphasized the practical value. In this country, it is Draper [5] who has sought to extend a wider appreciation of the medical importance of constitutional reactivity.

It is inflammation with which one is, after all, chiefly concerned. Whether one studies it in its physiologic approaches, as one can very readily in digestive activity, whether in the exaggerated or peculiarly modified manifestations apparent in allergy, whether in default, as it may be in severe infections, the fundamental components that control the phenomenon must be similar, must be amenable to control and, therefore, must be therapeutically approachable by other than specific measures. The fundamental components engaged include the local cell mass, the mobile cells, the vascular tissues, the autonomic nerves and the chemical and hormonic influences of the humoral milieu. The innumerable variations possible with so many variable factors operative in the process readily account for the different types of inflammatory reactions with which one has to deal clinically.

The emphasis on the etiologic factor in inflammation which resulted from the development of bacteriology, for a time over-shadowed any interest in factors that might inherently modify the inflammatory reaction. Only in relatively recent times does one find investigation dealing, for instance, with the modification of inflammation as the result of preexisting inflammatory processes (tuberculosis, for example), the change in the blood chemistry under such conditions or the gradual alteration of the autonomic responses.

The particular studies that are made the basis for this, as well as the subsequent related papers, have as their background the considerations outlined in the preceding paragraphs. We have taken a group of 100 so-called normal men and have endeavored to see what relation their reactions to a stimulus or an injury—blister, Kromayer lamp burn, ice, injection of epinephrine hydrochloride, pharmacologic intracutaneous injections, etc.—might bear to previous disease (tuberculosis, syphilis, infections), the blood chemistry, the basal metabolic rate, the age, the weight, etc.

There are many factors that limit the value of conclusions drawn from such work. In the first place, averages made from only 100 individual reactions are by no means satisfactory. The normal individual variations in many of the reactions are large. The possibility of error in the determination of many of the reactions themselves cannot be excluded, chiefly in such determinations as that of the basal metabolic rate. The practical inability to secure duplicates, due to the

4. Bauer, J.: Konstitutions und Vererbungslehre, ed. 2, Berlin, Julius Springer, 1923; Klin. Wchnschr. **8**:145, 1929.

5. Draper, George: Human Constitution, Philadelphia, W. B. Saunders Company, 1924.

fact that only one examination was feasible and that the amount of blood that could be taken without arousing resentment was limited, does not afford the feeling of accuracy that we might desire. These were factors that we could not alter, however much we might deplore them.

The persons examined were presumably "normal" men. That is to say, they were not patients of the hospital. About twenty were men employed about the hospital and laboratories as technicians, the rest were unemployed men who were sent to us from the state employment bureau. They ranged in age from 20 to 76; some were undernourished, some were chronic users of alcohol. A large percentage showed definite evidence of cardiorenal vascular damage of some degree. We felt that the group afforded us sufficient variation in reactivity because of their environmental conditions. We have not included women in the study lest the profound biologic alterations associated with the sex cycle [6] should introduce more factors difficult to evaluate and control.

EXAMINATIONS MADE

The men reported to us at eight in the morning, having been instructed to come without breakfast. In a few instances, they had had alcoholic stimulants the night before. Some were apprehensive and nervous, and the examination of the basal metabolic rate was undoubtedly unsatisfactory on that account. They were kept under observation the entire day, during which they were given a luncheon at noon.

The examinations made included the following:

1. The blood chemistry: calcium by the method of Clark and Collip; [7] potassium by the method of Kerr; [8] CO_2 combining power; sugar (Folin-Wu); cholesterol by the Bloor, Pelkan and Allen [8a] modification of the Bloor method; globulins by the method of Rohrer,[9] and total protein by the refractrometric method.

2. The skin blister by the cantharides method,[10] with determination of the relative permeability of the capillaries, and determination of the blister time.

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6. Petersen, W. F., and Milles, G.: The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, Arch. Int. Med. **38**:730 (Dec.) 1926.

7. Clark and Collip: J. Biol. Chem. **63**:461, 1925.

8. Kerr, J.: Biol. Chem. **67**:689, 1926.

8a. Bloor, W. R.; Pelkan, K. F., and Allen, D. M.: J. Biol. Chem. **52**:191, 1922.

9. Rohrer: Deutsches Arch. f. klin. Med. **121**:221, 1926.

10. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, Arch. Int. Med. **38**:663 (Dec.) 1926.

3. The basal metabolic rate and the weight/length ratio (weight in pounds, length in inches).

4. Reactions to the subcutaneous injection of epinephrine hydrochloride, as shown by pulse rate and blood pressure. In the charts, the increase or decrease in the average pulse pressure for one hour after the injection is recorded in terms of the percentage of the pre-injection level. A calculation was also made of the so-called cardiac output (pulse pressure $\times$ pulse rate), and the percentage of increase or decrease recorded.

5. The reaction to the Kromayer lamp, as shown in the time of appearance of erythema following an application of the light for thirty seconds to the forearm.

6. The reaction to ice, as revealed in the time of appearance of erythema following an application of ice to the chest wall.

7. The muscle reactions, as shown by the threshold of electric current that would provoke reactivity, in milliamperes.

8. The resistance of the moist skin for direct current of low amperage. This was determined in the following way:

A storage battery (fig. 1) of a potential difference of 2 volts was short circuited by a potentiometer of 730 Ω. From one terminal and the sliding contact of the potentiometer, a variable voltage could be taken between 2 volts and zero and measured by a scale along the potentiometer wire. This voltage was applied to the skin by two clay electrodes, soaked with 1 per cent saline solution. The larger electrode was kept firmly by the left hand of the patient, the smaller electrode was placed on those parts of the left arm the resistance of which was to be determined (from two to three on the front). Usually points close to the center of the biceps and those between the elbow and the wrist at the flexor side were selected. The resistance between the large electrode and the hand was negligible against the much larger resistance between the small electrode and the spots on the arm. Any contact between the smaller electrode and an open wound made it evident that the resistance of the lower tissues (muscle, blood vessels, etc.) was small as compared with the resistance of the skin. A micro-amperemeter was inserted in this circuit, one scale division registering 0.24 micro-ampere. All the readings were taken at scale division 10, i. e., 2.4 micro-amperes, by adjusting the potentiometer till this constant current was reached. This method employing constant current was preferable to the one employing constant voltage, because the resistance of the skin varied considerably, and sometimes, even with a low voltage, so much current was going through as to cause a burning, stinging pain; in this case, the current showed a tendency to go up gradually. In preparation for the measurements, the skin was wet with saline solution and then dried gently, and the wet electrode put on. The voltage was increased from zero to the one which gave a micro-amperage of 2.4. Exceptionally, the maximal voltage failed to cause the desired current to flow. In this case, the resistance was figured out from the voltage 2 and the current of less than 2.4 micro-amperes. Our figures for resistance are given in terms of megohms per square centimeter. Usually five spots on the biceps and five spots on the lower arm were measured. The measurements were made from three to

four times on the same day, early in the morning, right before and right after lunch and possibly later in the afternoon. This was important in order to get averages, and to gain an idea as to the variations that occur in the course of a day.[11] We have started investigations with the point of view of following up these variations of resistance more closely and in relation to other factors.

9. The reactions to intracutaneous injections (Hecht-Groer), as estimated by the average size of the wheal (diameter in millimeters) and

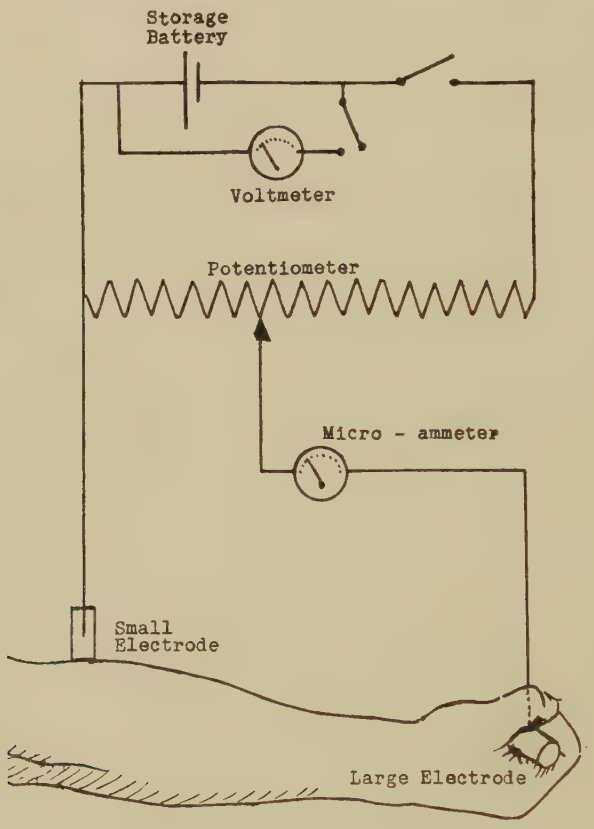

Fig. 1.—A diagram showing the method used in testing the resistance of the skin to electric current of low amperage.

11. Some measurements were repeated the next day or a few days later, in order to control variations that might occur from day to day. Extensive measurements of this kind were reported by Curt P. Richter (The Electrical Skin Resistance: Diurnal and Daily Variations in Psychopathic and in Normal Persons, Arch. Neurol. & Psychiat. **19**:488 [March] 1928). Richter found characteristic diurnal variations for certain classes of neurologic patients; daily variations occurred also, but they were small compared to the pronounced differences of the average resistance from one to another patient.

the flare (width of radium in millimeters) for: (*a*) morphine (1 to 10,000,000 and 1 to 1,000,000); (*b*) epinephrine hydrochloride, 1 to 1,000, 1 to 10,000, 1 to 100,000 and 1 to 1,000,000; (*c*) thyroxin, 1 to 10,000, and (*d*) caffein, 1 to 100.

10. A roentgenogram of the chest to ascertain the presence of active or healed tuberculosis and the condition of the great vessels and heart.

11. A physical examination and history, particular emphasis being laid on a history of sensitization and of previous infectious diseases, alcoholism, the amount of hard physical labor, etc.

12. A Wassermann test.

13. A urinalysis and examination of the skin capillaries.

METHOD OF ASCERTAINING CORRELATIONS

In order to obtain a general survey of the large amount of statistical material obtained, we proceeded in the following manner:

The results of each determination were arranged in arithmetical order. For instance, the individual cases were first arranged in the order of the time required for the formation of the blister, which varied from 3.5 to 15 hours. Four groups (twenty-five each) were then made, and the averages determined, the averages in this case being 5.8, 6.2, 7.9 and 10.2 hours. The averages were then recorded, and averages were determined and recorded for the results of the other examinations of the men thus grouped in order of increasing blister time. For instance, the corresponding averages for the time of the reaction to the application of the Kromayer lamp were found to be 1.27, 1.92, 2.4 and 2.36 hours, respectively, a sequence which might justify the supposition that some common factor is to be sought in the apparent coincidence of delay in the formation of the blister and delay in the appearance of the erythema. If, on the other hand, the averages for the results of the other examinations revealed no consistent progression or regression, we felt justified in assuming that no important correlation existed.

In table 1, we therefore present the average figures for each determination arranged in sequence, the four figures in each compartment indicating the averages of the four groups of twenty-five each.[12]

The heavy arrow has been inserted to show the direction of progression of the values for each key subject under consideration. Thus, column 1 indicates the average blister time of the four groups, and in reading down, the averages for the other determinations will be found. The lighter arrows indicate a probable correlation with the key sub-

12. Only the group arrangements for the flares of the reactions to thyroxin and caffein differ. Fifty-six persons have no thyroxin flares; the results for the rest were arranged in sequence. Sixty-four persons showed no caffein flares. The results for the thirty-six who showed flares were arranged in sequence in three groups of twelve each.

ject under consideration. Thus in column 1 some apparent relation exists between the calcium level, the potassium level, the K/Ca ratio, etc., and the subject under consideration, i. e., the blister time.

BLISTER TIME (TABLE 1, COLUMN 1)

The average blister time for the 100 men was 7.5 hours. In previous communications,[13] we called attention to the fact that the blister time of a person may vary considerably, being uniformly short in the exophthalmic patient and prolonged in patients with certain types of renal disease. In our use of the method, the plaster was removed after six hours, and the time of appearance of the blister recorded on the basis of the time from the application of the plaster to the time when the first evidence of blistering was observed. A shortening of the blister time was apt to be overlooked by this practice, and our records, therefore, are more accurate for the cases showing prolonged blister time than for those showing a shortened blister time.

The averages of the blister time (in hours) for the four groups, as recorded in table 1 are:

5.8 6.2 7.9 10.2

Certain correlations with other determinations appear as follows:

Kromayer Lamp Reaction Time.—The groups that had a long blister time showed a delay in the appearance of the erythema following application of the Kromayer lamp for 30 seconds, as follows (hours):

1.27 (ranging from 45 min. to 3 hrs.).
1.92 (ranging from 50 min. to 5 hrs., 50 min.).
2.4 (ranging from 1 hr., 10 min. to 8 hrs.).
2.36 (ranging from 1 hr., 25 min. to 4 hrs., 50 min.).

As the erythema is probably due to the liberation of toxic substances from the injured cells of the skin area (Lewis[14]), one might anticipate some correspondence. The agreement of the two reactions is confirmed when the cases are arranged according to the Kromayer lamp reaction time (column 9).

Basal Metabolic Rate.—With increasing blister time, the basal metabolic rate is lowered, but the sequence of regression is not perfect:

11.8 5.9 (9.8) 5.3

A general agreement with this trend is found in column 10.

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13. Petersen, W. F.: The Permeability of the Skin Capillaries in Clinical Conditions, Arch. Int. Med. **39**:19 (Jan.) 1927.

14. Lewis, Thomas: Blood Vessels of the Human Skin and Their Responses, London, Shaw & Sons, 1927.

Age.—Age plays some rôle, the group showing the prolonged bliser time being somewhat older, although the individual variations in the four groups are large:

46 yr.	44 yr.	43 yr.	53 yr.
(26-68)	(25-66)	(28-79)	(22-73)

When the results are arranged on the basis of age (column 19), the oldest age group again shows prolongation of the blister time. It is to be kept in mind that the oldest age group will show greater vascular-renal damage.

Calcium, Potassium and K/Ca Ratio.—The prolonged blister time seems to be associated with a higher level of the blood calcium, as is evident in the following values:

10	10.1	10.1	10.5

The corresponding values for potassium are in inverted order:

20.6	21.4	20.3	18

The K/Ca ratio is, as a result, much lower in the group showing prolonged blister time:

2	2.19	2.01	1.71

Globulin.—The group with prolonged blister time also has the greatest amount of serum globulin. The corresponding averages for the albumin/globulin ratios are:

2.1	2.22	2.18	1.73

This may be checked in column 8.

Summary.—An analysis of the material indicates that the group with prolonged blister time is somewhat older, has more globulin, more calcium and a lower K/Ca ratio and is less responsive to the Kromayer lamp.

PERMEABILITY (COLUMN 2)

The average index of capillary permeability for the entire group is 62. In our previous communications, we pointed out that the permeability of the capillaries, as measured by the blister method, is increased in certain persons, i. e., in those with exophthalmic goiter (13); in those with severe intoxications (13); in sympatheticotonic persons (15), etc. On the other hand, we noted that athletes tended toward a lower permeability (10), as did persons with certain types of lesions of the kidneys (13).

When the material now under consideration is grouped into the four groups of twenty-five each, the averages are found to be:

52	58	65	75
(46-56)	(56-61)	(61-70)	(70-91)

When the determinations are so grouped, the following correlations seem of interest:

Age.—Age apparently has a direct relation. The corresponding averages of the ages are:

51	50	46	41
(22-76)	(27-70)	(26-79)	(20-73)

It is obvious that all ages are represented in each group; nevertheless, the sequence is sufficiently good to seem of some significance (confirmed in column 19).

Weight.—Slender persons seemingly have the more permeable capillaries. The corresponding averages of the weight/length ratios are:

229	233	216	218

The confirmation in column 20 is good.

Reaction to Epinephrine.—In article IV,[15] we show that so-called sympatheticotonic persons have an increased permeability of the capillaries. In this grouping, it may also be observed that with increasing permeability, there is increased sensitivity to epinephrine. The values for the pulse pressures on injection of epinephrine hydrochloride averaged (per cent):

+9.4	+16	+12	+17

A confirmation of this appears in column 15.

Pulse Pressure.—With increasing permeability, the pulse pressure seems to diminish somewhat, the averages being:

55	53	54	50

corresponding to a slight decrease in systolic blood pressure.

Reactions to Intracutaneous Injection of Thyroxin and Caffein.—The flares of the reactions to thyroxin and caffein increase with increasing permeability (columns 27 and 29 may be compared with column 2 here).

Summary.—The apparent correlations are, therefore, with the age of the person, the weight/length ratio, the reaction to epinephrine, the pulse pressure and the radii of the thyroxin and caffein flares.

INFLAMMATORY INDEX (COLUMN 3)

In a previous study,[10] we sought to define an inflammatory index on the basis of the two determinations just discussed, i. e., the blister time and the permeability of the capillaries. Presumably, the degree of inflammation might be regarded as most intense if the rapidity of the

15. Article IV. The Relation of the Reaction to Epinephrine to Potassium/Calcium Ratio and to Other Ratios, p. 121.

reaction and the degree of protein passage through the vessels were taken into consideration. We therefore used the ratio permeability/blister time as an index and used the term inflammatory index for the quotient.

The average inflammatory index of the 100 men is 8.2

$$\frac{62 = \text{average permeability}}{7.5 = \text{average blister time}}$$

The averages for the four groups are:

5.7	8	9.4	10.9

The blood chemical correlations are evident:

Potassium Level.—

19.1	19.1	20.8	20.9

K/Ca Ratio.—

1.9	1.9	2.06	2.03

CO_2 Combining Power.—

56.5	57.3	57.3	58

These correlations are confirmed in columns 5, 6 and 17, respectively, though the confirmation in the latter case in only partial.

Albumin/Globulin Ratio.—Only the group with the low inflammatory index seems to have an increased amount of globulin, the ratios being:

1.4	2.5	1.8	2.3

and this is confirmed when the tabulations for globulin are examined (column 8).

Other Correlations.—The relation of age (the inflammatory index decreasing with age) seems certain; the relation of the weight/length ratio (a higher inflammatory index being found in the more slender subjects) is doubtful because it is not confirmed in column 20; and the correlation with the reactions to epinephrine is also uncertain for the same reason (columns 15 and 16). On the other hand, the resistance of the skin to electric current increases with increase in the inflammatory index, while the Kromayer lamp erythema time has a reverse relation (confirmed in column 9).

Summary.—We seem to be justified in the assumption that the inflammatory reaction to cantharides is inhibited by advancing age and is more intense with higher levels of potassium and higher values of the K/Ca ratio. The Kromayer lamp reaction time is comparable. There is a probability that the more slender persons and the persons with the more marked reactions to epinephrines have a more intense inflammatory reaction. Curiously enough, there appear to be no correlations

with the intracutaneous reactions to pharmacologic substances except that to thyroxin. This diminishes with increase in the inflammatory index (column 26).

CALCIUM (COLUMN 4)

The average calcium value for the 100 men is 10.17. The average calcium values for the four groups are:

9.2	9.7	10.8	12.2
(from 7.4-9)	(from 9.2-10.3)	(from 10.4-11.4)	(from 11.4-14.5)

Blister Time.—The relation to the blister time has been discussed.

Sugar Level.—There appears to be some relation to the sugar level, the persons with low calcium level having a lower sugar level (confirmed in column 7). The differences are not, however, great:

67	73	71	73

Resistance of the Skin to Electric Current.—A relation to the resistance of the skin to electric current seems probable (although the confirmation in column 11 is not convincing):

0.33	0.48	0.42	0.63

Reaction to Ice.—With an increasing amount of calcium, the reaction to ice is retarded (confirmed in column 18):

16	16.8	22.4	21.5

Pulse Rate, Systolic Blood Pressure, and Pulse Pressure—With increasing amounts of calcium, the pulse rate increases:

71	73	71	76

but the confirmation in column 14 is not good. The systolic blood pressure increases as follows:

121	123	122	129

but here, again, the confirmation (column 13) is not clear. The increase in the pulse pressure is more marked:

51	50	52	62

As no tabulation was made on the basis of pulse pressure, no confirmation is possible.

CO_2 Combining Power.—A possible correlation exists with the CO_2 combining power, which increases as follows:

56.4	57.8	57.5	57.9

These differences are not great, but appear to be confirmed in column 17, where the calcium values increase with increasing CO_2 values.

Skin Reactivity.—The calcium column is the first in which we begin to find some correlations with the reactions of the skin to injections of pharmacologic substances. The wheal caused by the injection of epinephrine hydrochloride increases progressively as follows:

17.2	19.2	20	20

The flare of the reaction to epinephrine also increases:

8	8.6	9.2	10

A confirmation of these increases is had in columns 22 and 23.

Summary.—The correlations of the level of the blood calcium are, therefore, with the following: blister time, blood sugar level, the resistance of the skin to electric current, the reaction to ice and the diameters of the wheal and flare of the reaction to epinephrine; and probably with the following: pulse rate, systolic blood pressure and pulse pressure, and CO_2 combining power.

POTASSIUM (COLUMN 5)

The average value of the blood potassium for the 100 men is 20.4. The fluctuations in the individual person's level of blood potassium are greater, as is well known, than those of the level of the calcium, changes of several milligrams per hundred cubic centimeters taking place during the course of the day. The normal range of values, too, is much greater, being from 13.4 to 28.8 mg. in our group.

Our four groups average:

16	18.2	20.4	25.7
(13.4-17.4)	(17.4-19)	(19-22.8)	(22.8-28.8)

Inflammatory Index.—The relation of the inflammatory index has already been mentioned.

CO_2 Combining Power.—With increasing potassium values, the CO_2 combining power appears to increase:

56.7	56.5	57.7	58.8

The confirmation in column 17 is, however, not striking.

Age.—The sequence is suggestive:

50	48	46	45

The expected confirmation in column 19 is, however, lacking.

Reaction to Epinephrine.—The pulse pressure shows a percentage increase with increasing amounts of potassium:

9.4	9.4	18.6	16.3

The pulse pressure $\times$ the pulse rate shows a percentage progress as follows:

15.4	16.8	28.4	23.2

which is confirmed for the pulse rate in column 15.

Muscle Reaction.—The group averages are:

3	3.4	3.6	2.66

a rather irregular sequence, but the control (column 12) is somewhat clearer:

21.9	19.6	20.5	18.7

Reaction to Thyroxin.—The most convincing correlations are those with the reactions of the skin to intracutaneous injections of thyroxin and caffeine. The wheals average (in millimeters):

12.2	11.4	11.6	9.2

This correlation is confirmed in column 26. The flares in the four groups average (in millimeters):

6.4	5.6	4.4	2.8

and this is confirmed in column 27.

Reaction to Caffein.—The wheals due to caffein show in similar relation:

20	20.4	18.6	11

confirmed in columns 28 and 29. The flares average:

2.8	4.8	3	1.6

Summary.—Apart from the distinct relation to the inflammatory index, the potassium values influence the reactions to epinephrine and the reaction of the skin to thyroxin and caffein; their relation to the CO_2 combining power, the muscle reaction and age are less certain.

THE K/CA RATIO (COLUMN 6)

The average value of the K/Ca ratios of the 100 men is 2. The averages for the four groups are:

1.45	1.81	2.35	2.66

Blister Time; Inflammatory Index.—The relations to the blister time and the inflammatory index have been discussed.

Resistance of the Skin.—A striking association exists with the resistance of the skin to electric current, the averages for which, in this grouping, are:

0.65	0.48	0.34	0.35

i. e., the groups with the increased K/Ca ratio have diminished resistance.

Reactions to Epinephrine.—The pulse pressures in the four groups average (per cent):

7.5	10	8.5	14

The values of the pulse pressure $\times$ pulse rate average (per cent):

14.6	14	17	24

This correlation is confirmed in columns 15 and 16.

Weight/Length Ratio.—The thinner persons have a lower K/Ca ratio:

205	219	217	222

Confirmation of this is had in column 20.

Cholesterol Level.—Those with low K/Ca ratio also appear to have less blood cholesterol:

215	220	218	229

This is confirmed in column 21.

Skin Reactions.—As might be expected from the potassium relations, the parallelism to the reactions of the skin to thyroxin and caffein is suggestive.

Summary.—The K/Ca ratio may, therefore, be regarded as of importance in connection with the blister time, the inflammatory index, the electrical resistance of the skin, the reactions to epinephrine, the weight/length ratio, the level of cholesterol and the reactions of the skin to thyroxin and caffein.

BLOOD SUGAR (COLUMN 7)[16]

The average of the blood sugar levels of the entire group is 71.

The four groups have the following averages:

60	68	74	82

Calcium Level.—The possible relation of the calcium level has been discussed.

Reactions to Epinephrine.—The most apparent correlation is with the reactions to epinephrine. The increase in pulse pressure for the groups is (per cent):

8.5	14	12	18

and the "cardiac output" (per cent) is:

13	21	22	29

This correlation is confirmed in columns 15 and 16.

Weight/Length Ratio.—As the sugar increases, the weight also increases:

205	219	217	222

This is confirmed in column 20.

The Flares Caused by the Intracutaneous Injection of Epinephrine Hydrochloride.—The averages for the groups are (in millimeters):

7.6	8.4	8.4	9

This correlation is confirmed in column 23.

16. The sugar values are for serum.

Summary.—The following correlated factors are, therefore, to be considered: The level of the blood calcium, the sensitivity to epinephrine, the weight/length ratio and the reaction of the skin to epinephrine.

ALBUMIN/GLOBULIN RATIO (COLUMN 8)

The average value of the albumin/globulin ratio for the entire group is 2. The averages for the four groups are:

1.1	1.6	2.08	3.3

Blister Time.—It has been previously noted that increasing blister time is associated with an increased amount of globulin. This seems confirmed by the fact that the first group under consideration here with a ratio of 1.1 has a blister time of nine hours.

Muscle Reactivity.—A good correspondence is found:

2.9	2.8	3.1	4

and this correspondence is confirmed in column 12.

Reactions of the Skin to Epinephrine and Thyroxin.—The amount of flare due to the epinephrine is apparently associated:

8	8.2	9	9.2

This association is confirmed in column 23.

The averages for the wheals caused by the intracutaneous injection of thyroxin are:

11	11.6	11	12.6

These seem related (confirmed in column 26), as also those for the flares caused by thyroxin and for the wheals caused by caffein.

Summary.—An increased amount of globulin is, therefore, probably related to an increased blister time, to an increased muscle irritability and to the reactions of the skin to epinephrine, thyroxin and caffein.

KROMAYER LAMP ERYTHEMA TIME (COLUMN 9)

For the 100 men, the average time of the appearance of the erythema from the time of application of the Kromayer lamp is 2 hours. The averages for the four groups are (hours):

1.24	1.58	1.95	3.3
(75 min.)	(96 min.)	(117 min.)	(200 min.)

Blister Time and Inflammatory Index.—The parallelism with the blister time and the inflammatory index has been discussed.

Calcium Level.—The apparent relation to calcium is:

10.3	10.1	9.9	9.7

but there is no confirmation in column 4.

CO_2 Combining Power.—The relation to the CO_2 combining power may be seen in the following averages:

55.8 55 58 58.8

This correlation is confirmed in column 17.

Wheal Caused by Epinephrine.—The averages are:

20.4 20.4 20.4 18.4

Only the group with the long latent period appears to have some relation to the smaller wheal, the confirmation of this being found in column 22.

Summary.—The associations of the time of the erythema due to application of the Kromayer lamp appear to be the following: the blister time, the inflammatory index, the CO_2 combining power and the diameter of the wheal caused by epinephrine.

BASAL METABOLIC RATE (COLUMN 10)

The average basal metabolic rate for the entire number is +8. The averages for the groups are:

—8.9 +2.2 +13.3 +28

Reaction to Ice.—The reaction to ice as shown in the following averages, clearly parallels the basal rate:

16.3 19.3 20 20.4

and the parallelism in column 18 is equally good.

Resistance of the Skin to Electric Current.—As the basal rate increases, the resistance of the skin to electric current appears to decrease, although the sequence is not perfect:

0.47 0.39 (0.62) 0.3

Weight/Length Ratio.—A correlation appears to exist with the weight/length ratio, the more slender persons having the higher rate:

221 219 216 207

This is confirmed in column 20.

Skin Reaction.—The wheal due to epinephrine diminishes with the increased metabolic rate:

19.2 20 18.8 15.2

This is confirmed in column 22.

Summary.—The basal metabolic rate, therefore, appears to be correlated with the electrical resistance of the skin, the reaction to ice, the weight/length ratio and the diameter of the wheal due to epinephrine.

RESISTANCE OF THE SKIN TO ELECTRIC CURRENT (COLUMN 11)

The average resistance for the 100 men is 0.46 megohms per square centimeter. The averages for the four groups are:

0.14 0.27 0.40 1.03

Inflammatory Index, Calcium, K/Ca Ratio and Metabolic Rate.—The parallelisms here have been discussed.

Muscle Reaction.—A higher resistance of the skin appears to be associated with a lower threshold response of the muscle, the averages being:

3.6	3.5	2.5	2.7

This association is confirmed in column 12.

Weight/Length Ratio.—The thinner persons have a high resistance:

220	230	217	200

This is confirmed in column 20.

Skin Reaction.—The flare due to epinephrine increases with the resistance of the skin to electric current:

8.4	8.6	8.4	9.8

This is confirmed in column 23.

The flare caused by thyroxin averages:

3.4	5.2	5.2	5.6

The correlation is confirmed in column 27.

Summary.—The resistance of the skin to electric current has associations with the inflammatory index, the K/Ca ratio and the level of calcium, the metabolic rate, the muscle reaction, the weight/length ratio, the amount of flares due to epinephrine and thyroxin, and possibly the permeability of the capillaries.

MUSCLE REACTIVITY (COLUMN 12)

The average for the muscle reactivity of the whole number is 3.2 milliamperes. The averages for the four groups are:

1.7	2.3	3.66	6.1

Albumin/Globulin Ratio and Skin Resistance.—The relations here have been discussed.

Pulse Rate.—The pulse rate diminishes as the muscle reactivity diminishes:

78	74	68	70

This relationship is checked in column 14.

CO_2 Combining Power.—One should anticipate a distinct decrease in the CO_2 combining power with decreasing reactivity. The results recorded in the table, however, indicate the opposite. The control is also irregular.

Weight/Length Ratio.—The weight/length ratio increases with the muscle reactivity:

207	221	228	224

This increase is confirmed in column 20.

Reaction to Caffein.—The wheal due to the intracutaneous injection of caffein increases in diameter with increase in muscle reactivity:

15.8 — 18.8 (17.4) 19.6

The parallel increase is checked in column 28.

Summary.—In addition to the correlations with the albumin/globulin ratio and the skin resistance, correlations with the following seem possible: the pulse rate, the weight/length ratio and the diameter of the wheal due to caffein.

SYSTOLIC BLOOD PRESSURE (COLUMN 13)

The average blood pressure for the whole number is 124 systolic and 71 diastolic. The averages for the four groups are:

104 — 118 128 146

Diastolic Blood Pressure and Pulse Pressure.—Naturally the diastolic blood pressure corresponds:

62 70 72 76

as well as the pulse pressure:

42 58 56 68

Reaction to Epinephrine.—The pulse pressure, as well as the pulse pressure × pulse rate, is distinctly associated with the systolic blood pressure, the averages being (per cent):

21 12 9.9 9.4
27 20 18 16

Age.—The age increases with the systolic pressure:

45 (43) 46 54

This correlation is checked in column 19.

Reaction to Caffein.—The flare diminishes:

7.6 3 2.2 3.8

This is confirmed in column 29.

Summary.—The associations (apart from those with diastolic and pulse pressure) apparently are with the following: the reaction to epinephrine, the age and the radius of the flare due to the intracutaneous injection of caffein.

PULSE RATE (COLUMN 14)

The average pulse rate for the 100 men is 72.5. The averages for the four groups are:

60 69 76 86

Calcium Level and Muscle Reaction.—The relations here have been discussed.

Reaction to Epinephrine; CO_2 Combining Power.—The apparent correlations with the "cardiac output" following epinephrine injection and with the CO_2 combining power are not confirmed in columns 16 and 17.

Reaction to Caffein.—The averages for the wheal are:

18	(19.4)	17.8	16

This relation is confirmed in column 28.

Summary.—The correlations appear to be with the following: the level of calcium, the muscle reaction, the reaction to caffein, and possibly with the CO_2 combining power and the reactions to epinephrine.

REACTIONS TO EPINEPHRINE: EFFECT ON PULSE PRESSURE (COLUMN 15)

The average increase of the pulse pressures of the 100 men is + 14.7 per cent during the hour following injection. The increase or decrease (per cent) for the four groups is:

—3.5	+6	+16	+36

Permeability of Capillaries, Potassium Level, K/Ca Ratio, Sugar and Systolic Blood Pressure.—The relations here have been discussed.

Pulse Pressure.—The persons with the greatest reaction to epinephrine are in the group who have the smallest pulse pressures before the injection:

54	56	50	42

There is no confirmation here because no results are arranged on the basis of pulse pressure.

Cardiac Output.—The correlation is such as might be expected.

Weight/Length Ratio.—The more slender men show the greater reaction to epinephrine:

225	216	215	197

This is partially confirmed in column 20.

Summary.—The chief correlations are, therefore, with the permeability of the capillaries, the potassium level, K/Ca ratio, the sugar level, the systolic blood pressure and the weight/length ratio.

REACTIONS TO EPINEPHRINE (COLUMN 16): "CARDIAC OUTPUT" (PULSE PRESSURE × PULSE RATE)

The average increase of the "cardiac output" of the 100 men is 20.5 per cent. The increase (per cent) for the four groups following the injection of epinephrine hydrochloride is as follows:

—1.7	+19	+24	+42

K/Ca Ratio, Sugar, Reaction to Epinephrine (Pulse Pressure).—The correlations here have been discussed.

CO_2 Combining Power.—The correlation with the CO_2 combining power is good:

57.4 57.8 57.9 59.5

but the control (column 17) does not check.

Reactivity to Epinephrine.—The flares averaged (in millimeters):

8.6 8.6 9.2 9.6

The control may be read in column 23.

Summary.—Only a few correlations can, therefore, be ascertained: these are with the K/Ca ratio, the sugar level and the diameter of the flare due to epinephrine, and, possibly, with the permeability of the capillaries and the CO_2 combining power.

CO_2 COMBINING POWER (COLUMN 17)

The average CO_2 combining power of the 100 men is 57.7. The averages for the four groups are:

53.5 56.5 58 62.3

Kromayer Lamp Erythema Time.—The correlations have been commented on previously.

Reaction to Ice.—The reaction time increases with the increase in CO_2 tension, the averages being as follows:

17 20 19 19

The control (column 18) affords some support.

Weight/Length Ratio.—A distinct correlation exists here, the more slender men having a higher CO_2 combining power:

229 218 210 212

Reaction to Thyroxin.—The amount of flare of the reaction to thyroxin seems related:

6.4 3.4 5. 4.4

The confirmation appears in column 27.

Summary.—The apparent correlations are with the weight/length ratio, the reaction to ice, the Kromayer lamp erythema time and the amount of flare in the reaction to thyroxin.

ICE REACTION TIME (COLUMN 18)

For the 100 men, the average time of the reactions to ice is nineteen seconds. The averages for the four groups are (seconds):

9 15 20 32

Calcium, Basal Metabolic Rate, CO_2 Combining Power.—The correlations with these have been discussed.

Age.—The relation to age is obvious:

44	45	48	49

This relation is confirmed in column 19.

Skin Reactions.—A possible relation exists to the radius of the flare in the reaction to thyroxin and to the dimensions of both wheal and flare in the reactions to caffein. The averages for the former are:

5.8	5	5.4	2.6

This is confirmed in column 27.

The averages for the wheal and the flare of the reaction to caffein are:

20.6	18.2	18.8	14
2.4	2.2	3.4	3

These correlations are confirmed in column 28 and column 29, respectively.

Summary.—The correlations are, therefore, with the age, the level of the calcium, the basal metabolic rate, the CO_2 tension, the radius of the flare of the reaction to thyroxin and the dimensions of both the wheal and the flare of the reactions to caffein.

AGE (COLUMN 19)

The average of the ages of the 100 men is 46.5. The averages for the four groups are:

30	42	51	65

Blister Time, Permeability of Capillaries, Inflammatory Index, Systolic Blood Pressure, Reaction to Ice.—The correlations here have been discussed.

Reaction to Caffein.—There is some indication that the diameter of the wheal increases with the age:

14.6	13.4	21	21.4

The confirmation of this is in column 29.

Summary.—The correlations are with the blister time, the permeability of the capillaries, the inflammatory index, the potassium level, the blood pressure, the reaction to ice and the reaction to caffein.

WEIGHT/LENGTH RATIO (COLUMN 20)

The average of the weight/length ratios of the 100 men is 217. The averages for the four groups are:

187	207	216	232

Permeability of Capillaries, K/Ca Ratio, Sugar Level, Basal Metabolic Rate, Skin Resistance, Muscle Reaction, Reactions to

Epinephrine and CO_2 Combining Power.—The correlations here have been commented on.

Cholesterol Level.—The averages for cholesterol show a relation (confirmed in column 21) as follows:

210 217 216 225

Skin Reactions.—The diameters of the wheals in the reactions to epinephrine average (in millimeters):

18.8 18.8 19.6 20

This correlation is confirmed in column 22.

The flares of the reactions to the intracutaneous injection of morphine average (in millimeters):

14.8 15 16.6 15.8

This parallel increase is confirmed in column 25.

Summary.—The correlations in this grouping are seemingly most extensive.

CHOLESTEROL (COLUMN 21)

The average of the cholesterol values for the entire number examined is 207. The average for the groups are:

181 219 202

Only three groups were arranged because determinations of cholesterol were not made for the entire series.

Correlations.—The correlations are with the K/Ca ratio and the weight/length ratio. It appears that the pulse pressure also bears some relation, diminishing as the cholesterol increases. The correlations are, therefore, few.

REACTIONS TO EPINEPHRINE: THE WHEAL (COLUMN 22)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of epinephrine hydrochloride is 19.2 mm. The averages for the groups are:

16.8 17.6 20.4 22.

Calcium Level, Basal Metabolic Rate, Weight/Length Ratio, Kromayer Lamp Reaction Time.—We have previously called attention to the possible correlations here.

Pulse Pressure.—The pulse pressure seemingly increases with the size of the wheal:

51 50 56 56

No check is possible, however.

Reaction to Caffein.—The averages of the diameters of the wheals indicate a relation (checked in column 28):

(18) 20.2 19.4 13.2

Summary.—The correlations are, therefore, with the calcium level, the basal metabolic rate, the weight/length ratio, the Kromayer lamp erythema time and the reactions to caffein.

REACTION TO EPINEPHRINE: THE FLARE (COLUMN 23)

The average of the radii of the flares in the reactions of the 100 men to epinephrine is 8.8 mm. The averages for the groups are:

5.8	8.8	10	11.6

Calcium, Sugar, Albumin/Globulin Ratio, Skin Resistance, Reaction to Epinephrine (Pulse Pressure × Pulse Rate).—The correlations with these have been previously discussed.

Reactions to Morphine Flare.—The flares of the reactions to morphine show a parallel increase (checked in column 25):

13.2	15	16	16.6

Reactivity to Caffein.—The wheals in the reactions to caffein also show a relation (checked in column 28):

18	19.4	18.6	14.4

Summary.—The relations are, therefore, to the calcium level, the sugar level, the albumin/globulin ratio, the skin resistance, the reaction to epinephrine (pulse pressure × pulse rate) and the reaction to morphine (flare) and to caffein (wheal).

REACTION TO MORPHINE: THE WHEAL (COLUMN 24)

The average of the diameters of the wheals in the reactions of the 100 men to intracutaneous injections of morphine is 12.4 mm. The averages for the four groups are:

9	10.6	11.8	14.

No correlations are found.

REACTION TO MORPHINE: THE FLARE (COLUMN 25)

The average of the radii of the flares in the reactions of the 100 men to morphine is 15.6 mm. The averages for the groups are:

10	14.4	16.6	22

The correlation with the weight/length ratio has been referred to. The amount of flare in the reaction of the skin to epinephrine is apparently related:

7.8	8.8	9.6	10

REACTION TO THYROXIN: THE WHEAL (COLUMN 26)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of thyroxin is 13.6 mm. The averages for the groups are:

7.6	10.4	12	14.6

Inflammatory Index, Potassium, K/Ca Ratio, Albumin/Globulin Ratio.—The correlations here have been discussed.

Reaction to Thyroxin (Flare).—The averages for the flares are:

2.6 3.6 6.6 6.2

This may be checked in column 27.

Reaction to Caffein.—The averages for the wheals in the reactions to caffein are:

8.6 19 22.2 20.6

for the flares:

1.2 2.4 2.8 4.2

These parallel increases may be checked in columns 28 and 29, respectively.

Summary.—The correlations, therefore, are with the inflammatory index, the potassium level, the K/Ca ratio, the albumin/globulin ratio, the amount of flare in the reaction to thyroxin and the reaction to caffein (wheal and flare).

REACTION TO THYROXIN: THE FLARE (COLUMN 27)

The average of the radii of the flares in the skin reactions of the 100 men to thyroxin is 4.8 mm. The averages for the four groups are:

0 4.6 8.6 10.6

In this grouping, fifty-six men showed no reaction to the thyroxin. These fifty-six are represented by zero; the other three groups, consisting of 18, 19 and 19 men each, showed flares as set forth.

The averages for the wheals in the reactions to caffein (checked in column 28) are as follows:

16.3 15. 20.8 20.2

for the flares:

0.8 4.6 2 5.8

Correlations.—Previously discussed correlations include those with the potassium level, the K/Ca ratio, the resistance of the skin to electric current, the reaction to ice, the reaction to epinephrine (wheal) and the size of the wheal in the reaction to thyroxin. It is to be noted that the caffein reaction is closely related.

REACTION TO CAFFEIN: THE WHEAL (COLUMN 28)

The average of the diameters of the wheals in the reactions of the 100 men to the intracutaneous injection of caffein is 17.6 mm. The averages for the four groups are:

7.6 15.2 21.6 25

Correlations previously discussed include those with the potassium level, the K/Ca ratio, the reaction to ice, the albumin/globulin ratio, the muscle reaction, the pulse rate, the age and the reaction of the skin to epinephrine (wheal and flare) and to thyroxin (wheal and flare).

REACTION TO CAFFEIN: THE FLARE (COLUMN 29)

The average of the radii of the flares in the reactions of the 100 men to caffein is 2.75 mm. The averages for the groups are:

0	4	7.4	11

In this grouping, sixty-four men gave no flares. They are represented by the zero. The other three groups, consisting of twelve men each, gave flares averaging as set forth.

TABLE 2.—*The Relations of the Blister Time, the Inflammatory Index and the Kromayer Lamp Erythema Time to Mineral Balance and Other Factors*

	Blister Time, Increasing ⟶	Inflammatory Index ⟵	Kromayer Lamp Erythema Time, Increasing ⟶
Calcium level	⟶	....	(⟵)
Potassium level	⟵	⟶	⟵
K / Ca ratio	⟵	⟶	⟵
CO_2	....	⟵	⟶
Muscle reaction	....	....	⟶
Albumin / globulin ratio	⟵	(⟵)	....
Basal metabolic rate	⟵	(⟶)	....
Vascular reaction to epinephrine	⟵	(⟵)	⟵
Skin reaction to epinephrine	....	....	⟵
Resistance of skin to electric current	....	⟵	....
Weight / length ratio	⟵	⟶	⟵

Correlations with the permeability of the capillaries, the systolic blood pressure, the reaction to ice, the age and the reaction to thyroxin (wheal and flare) have been previously discussed.

COMMENT

Blister Time, Inflammatory Index, Kromayer Lamp Erythema Time.—That the reactivity of the skin to cantharides, as estimated by the blister time, the inflammatory index and the reaction time to the Kromayer light, is closely associated with the mineral balance becomes apparent in table 2.

The agreement concerns chiefly the potassium level, the K/Ca ratio and the weight/length ratio. The blister time and the reaction time to the Kromayer light are, furthermore, in alinement with relation to the vascular reaction to epinephrine.

If one classifies the men examined on the basis of the vascular reaction to epinephrine, one must conclude that vagotonic (lessened or negative) reaction to epinephrine is associated with prolonged blister time and prolonged Kromayer lamp erythema time.

Permeability of the Capillaries, Inflammatory Index.—We turn next to another factor of the inflammatory index, permeability of the capillaries. In table 3 a comparison of this factor with mineral balance and other factors is made. The correlationship with the reaction time to the Kromayer light falls away because there is no apparent direct relationship between this and permeability of the capillaries. Here it again becomes evident that the K/Ca ratio, the CO_2 combining power, the

TABLE 3.—*The Relations of Permeability of the Capillaries and Inflammatory Index to Mineral Balance and Other Factors*

	Permeability of Capillaries ⟶	Inflammatory Index ⟶
Calcium level	(?) ⟶	.....
Potassium level	.....	⟶
K / Ca ratio	⟵	⟵
CO_2	⟶	⟶
Muscle reaction	.....	.....
Albumin / globulin ratio	⟶	⟶
Basal metabolic rate	.....	⟵
Age	⟵	⟵
Vascular reaction to epinephrine	⟶	(⟶)
Skin reaction to epinephrine	.....	.....
Skin resistance to electric current	⟶	⟶
Weight / length ratio	⟵	⟵
Reaction to thyroxin and caffein (flares)	⟶	.....

albumin/globulin ratio, the age, the weight/length ratio and the resistance of the skin to electric current are related.

From tables 1 and 3, it is obvious that permeability of the capillaries of the skin, while related to the K/Ca ratio, appears to be less under the influence of the actual concentrations of these elements. There is a clear relation to age, to the vascular responsiveness to epinephrine, to the resistance of the skin to electric current and to the weight/length ratio.

Variations of the endocrine status, particularly as concerns thyroid activity, are probably chiefly concerned. The younger person has presumably greater secretory activity, greater permeability of the capil-

laries and a more marked sensitivity to epinephrine. The width of the flares in the skin reaction to thyroxin and caffein forms part of this picture.[17]

In table 4 the various factors that have been examined are grouped as they relate to skin reactivity. When one examines this table, a number of consistent correlations immediately stand out:

The increase in permeability of the capillaries proceeds with an increase in the inflammatory index and in the flares due to epinephrine, thyroxin, caffein and morphine (not shown in table).

Increase in the serum calcium is associated with (1) a prolonged reaction time to ice, but with a diminished reaction time to the Kromayer light; and (2) an increase in the size of the wheal and the flare due to epinephrine, but a decrease in the size of the wheal due to thyroxin. These contrary reactions to epinephrine and thyroxin have been observed previously.[17]

Increase in potassium proceeds with (1) an increase in the inflammatory index, but is associated with a prolongation of the erythemas due to the application of the Kromayer light and ice; and (2) a decrease in the size of the wheals and flares due to thyroxin and caffein.

Increase in the K/Ca ratio proceeds with (1) an increase in the inflammatory index, but a delay in the reaction to ice, and (2) an increase in the reactions to thyroxin and caffein as the K/Ca ratio is lowered.

Increase in the CO_2 combining power of the serum (in the direction of an alkalosis) accompanies (1) increase in the inflammatory index and increase in the time of erythema due to the applications of the Kromayer light and ice; and (2) increase in the wheal due to epinephrine and decrease in the wheal due to thyroxin.

Increase in the basal metabolic rate accompanies (1) increase in the inflammatory index, shortening of the reaction to the Kromayer light and prolongation of the reaction to ice, and (2) decrease in the wheal and flare due to epinephrine.

As the weight/length ratio increases (in heavier persons), the wheal due to epinephrine increases in size, while the wheal due to thyroxin tends to diminish.

Table 5 presents the blood chemistry and its correlations with the weight/length ratio and other factors. When one examines this table on the basis of the weight/length ratio, one finds that as weight increases, four reactions may be grouped: 1. Permeability of the capillaries diminishes. 2. Potassium increases. 3. The K/Ca ratio increases. 4. The CO_2 combining power diminishes.

17. Article V. The Patient with Exophthalmos and the Nervous Patient, p. 135.

TABLE 4.—*The Relations of the Various Factors Examined to Skin Reactions*

	Inflammatory Index	Reaction to Kromayer Light	Reaction to Ice	Skin Reactions: Epinephrine, Wheal	Epinephrine, Flare	Thyroxin, Wheal	Thyroxin, Flare	Caffein, Wheal	Caffein, Flare
Blister time	--	+	--	--	--	+	+	--	--
Permeability of capillaries	+	--	--	--	+	--	+	--	+
Inflammatory index		+	--	--	--	+	--	--	--
Calcium level	--	+	+	+	+	+	--	--	--
Potassium level	+	--	+	--	--	+	+	+	+
K / Ca ratio	+	--	+	--	--	+	+	+	+
CO_2 combining power	+	+	+	+	--	+	+	--	--
Sugar level	--	--	+?	+	+	--	--	--	--
Albumin / globulin ratio	--	--	--	+	+	+	+	+	--
Vascular reaction to epinephrine	+	--	--	--	+	--	--	--	--
Skin resistance to electric current	+	--	+	--	+	--	--	--	--
Basal metabolic rate	+	+	+	+	+	--	--	--	--
Muscle reaction	--	+	--	--	+	--	+	+	--
Blood pressure	--	--	--	--	--	+	--	+	+
Age	+	--	+	--	--	--	--	+	--
Weight / length ratio	--	--	--	+	--	+	+	+	--
Reaction to ice	--	--		+	--	--	+	+	+
Reaction to Kromayer light	+		--	+	--	--	--	--	--

TABLE 5.—*The Blood Chemistry and Its Correlations with the Weight/Length Ratio and Other Factors*

	Weight / Length Ratio	Vascular Reaction to Epinephrine	Sugar Level	Muscle Reaction	Pulse Rate	Blood Pressure	Reaction to Epinephrine, Wheal	Reaction to Epinephrine, Flare	Reaction to Thyroxin, Wheal	Reaction to Thyroxin, Flare
Inflammatory index	--	--	--	--	-	--	--	--	+	--
Permeability of capillaries	+	+	--	--	+	--	--	+	+	+
Calcium level	--	--	+	--	+?	--	+	+	+	--
Potassium level	+	+	--	+	--	--	--	--	+	+
K / Ca ratio	+	+	--	+	--	--	--	--	+	+
CO_2 combining power	+	--	--	--	+?	--	+	--	+	+
Albumin / globulin ratio	--	--	+	+	+	--	--	+	+	+
Basal metabolic rate	+	--	--	--	--	--	+	+	--	--
Skin resistance	+	--	--	+	--	--	--	+	--	--
Muscle reaction	+	--	--		+	+	--	+	--	--
Sugar level	+	+		--	--	--	+	+	--	--
Age	--	--	--	--	--	+	--	--	--	--
Weight / length ratio		+	+	+	--	+	+	--	--	--
Pulse rate	--	--	--	+		+	--	--	--	--
Blood pressure	--	+	+	--	--		--	--	--	--
Reaction to ice	--	--	--	--	--	--	+	--	+	+
Kromayer lamp erythema time	--	--	--	--	--	--	+	--	--	--
Vascular reaction to epinephrine	+		+	--	+	+	--	+?	--	--
Reaction to epinephrine, wheal	+	--	--	--	--	--		--	+	--
Reaction to epinephrine, flare	--	--	+	--	--	--	--		+	+
Reaction to thyroxin, wheal	--	--	--	--	--	--	--	--		+
Reaction to thyroxin, flare	--	--	+	-	--	--	+	--	+	

This group of chemical correlations is distinctly related to the wheal and flare due to thyroxin, both of which diminish with increasing weight.

With the increase in weight, the second group of reactions is to be studied: 1. The basal metabolic rate diminishes. 2. The resistance of the skin to electric current increases. 3. The muscle reactivity diminishes. 4. The sugar increases.

This second group of reactions is not so closely related to the K/Ca ratio (muscle reaction is related to the potassium level, and the sugar to the calcium), but it shows a distinct correlation with the skin reactions to epinephrine. The wheal of the latter increases with increasing weight, and with lowered metabolic rate; the flare diminishes.

If one wishes to use the term sympatheticotonic or vagotonic, one can say that the heavy group is the parasympathetic group, and the thin group the sympatheticotonic. We do not, however, believe that these terms are justifiable or helpful, because there are too many divergent autonomic reactions. (Table 6.)

TABLE 6.—*The Relation to Weight*

Heavy Persons		Thin Persons
Low	Permeability of the capillaries	High
High	Potassium	Low
High	K / Ca ratio	Low
Low	CO_2	High
Low	Basal metabolic rate	High
Low	Skin resistance to electric current	High
Low	Muscle reactivity to electric current	High
Low	Reaction to epinephrine (pulse pressure)	High
Increased	Reaction to epinephrine, wheal	Diminished
Increased	Reaction to epinephrine, flare	Diminished
Diminished	Reaction to thyroxin, wheal	Increased
Diminished	Reaction to thyroxin, flare	Increased
Increased	Cholesterol	Decreased

The age of persons plays relatively little rôle in the reactivities that we have studied. The blood pressure is, of course, increased and the inflammatory index is lowered, as is the permeability of the capillaries. The reaction to ice, too, is somewhat delayed in old age.

EXPLANATION OF TERMS USED

Blister Time.—The time in hours for the formation of a blister on the forearm following the application of a cantharides plaster.

Permeability of Capillaries.—The ratio of the protein in the blister to the protein in the capillary blood.

Albumin/Globulin Ratio.—Method of Naegele.

Kromayer Erythema Time.—The time in hours for the first appearance of erythema following a thirty-second exposure of the forearm to the Krohmayer lamp.

Skin Resistance.—The resistance of the skin of the forearm to the passage of a direct current of electricity.

Muscle Reaction.—Muscle reaction (CCC).

Epinephrine Reaction.—The average percentage increase or decrease from the preinjection level of the pulse pressure for one hour after the injection.

Epinephrine Reaction.—The average percentage increase or decrease from the preinjection level of the pulse pressure times pulse rate for one hour after the injection.

Ice Reaction.—The time in seconds for the appearance of an erythema following a transient application of ice to the chest wall.

Weight/Length Ratio.—The weight in pounds divided by the length in inches.

Intracutaneous Reactions to Pharmacologic Substances.—The size of the wheal and of the flare (in mm.) at the site of the intracutaneous injection of epinephrine hydrochloride 1 : 1,000,000, 1 : 100,000, 1 : 10,000 and 1 : 1,000; morphine 1 : 10,000,000 and 1 : 1,000,000; thyroxin 1 : 10,000 and caffein 1 : 100.

II. THE CLINICAL STATUS OF THE GROUP OF ONE HUNDRED "NORMAL" MEN

In the first part of the study, we presented a table of possible correlations of certain reactions of the skin (the blister time, the reaction time to the Kromayer light, the reaction time to ice, the resistance of the skin to electric current, the reactions to intracutaneous injections of pharmacologic substances, etc.) with the blood chemistry.

In the present analysis of this material, we proceed to a grouping of the men into clinical subdivisions, based on the physical observations and on the results of the urinalyses, the examinations of the blood pressures, the Wassermann tests, the roentgenologic interpretations, the microscopic examinations of the capillaries of the skin, etc.

In arranging the individual results of the examinations of these men, we first present table 1, which classifies the men as follows: a normal group of 20 men (column 3); a group of 9 proved by the x-rays to have active tuberculosis (column 4); a group of 17 with healed parenchymal tuberculosis, as evidenced by the x-rays (column 5); a group of 4 with syphilis (column 6); a group of 40 with cardiovascular renal disease, which has been subdivided to include those with arteriosclerosis, as shown by the x-rays (column 7), those with probable myocarditis, as shown by the x-rays (column 8), those with an increased range of blood pressure (column 9), those with a normal range of blood pressure (column 10), those with a low range of blood pressure (column 11), those with changes in the urine—casts or albumin (column 12) and those with alterations of the capillaries of the skin—granulation, tortuosity, slowing, etc. (column 13); a sensitized group of 2 (column 15); a "nervous" group of 4 (column 16), and a group of 4 with miscellaneous conditions, making a total of 100 men.

The following tables have been prepared: Table 2 contains the results of the examinations of the normal men; table 3, of men with roentgen evidence of healed tuberculosis, and table 4, of men with roentgen evidence of active tuberculosis.

The cardiovascular renal material has been recorded in the following way: in table 5, the results of the examinations of men with increased blood pressure, but without urinary changes; in table 6, of men with increased blood pressure with urinary changes; in table 7, of men with normal blood pressure and normal urine, but with x-ray evidence of arteriosclerosis or myocarditis; in table 8, of men with normal blood pressure, but with urinary changes; in table 9, of men with blood pressure under 110 (including the syphilitic group, normal men and men with roentgenologic evidence of healed tuberculosis), and in table 10, of men with low blood pressure, but with urinary changes.

The averages for these groups have been brought together in table 11.

TABLE 1.—*Classification of One Hundred So-Called Normal Men on the Basis of the Results of Physical Examinations*

Serial Number	Individual Number	Normal Persons	Tuberculosis, Shown by Roentgenogram: Active	Tuberculosis, Shown by Roentgenogram: Healed	Syphilis	Cardiovascular Renal: Arteriosclerosis of Large Vessels (X-Ray)	Cardiovascular Renal: Myocarditis (X-Ray)	Cardiovascular Renal: Blood Pressure: High	Cardiovascular Renal: Blood Pressure: Normal	Cardiovascular Renal: Blood Pressure: Low	Cardiovascular Renal: Changes in Urine (Casts or Albumin)	Cardiovascular Renal: Changes in Skin Capillaries	Cardiovascular Renal: Cardiovascular Renal	Sensitized	Nervous	Miscellaneous	
1	3	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
2	4	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
3	8	1	..	..	..	..	..	..	..	..	.	..	..	..	..	..	
4	10	..	..	1	..	..	..	..	..	..	..	..	..	..	.	..	
5	13	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
6	14	..	..	..	..	..	..	..	+	..	+	..	1	..	..	..	(Liver)
7	15	..	..	1	..	..	..	..	..	..	..	..	..	..	.	..	
8	17	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
9	18	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
10	20	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	
11	21	..	..	+	..	..	..	+	..	..	..	+	1	..	..	..	
12	23	..	..	1	..	..	..	..	..	+	..	..	..	.	..	..	
13	24	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
14	25	..	1	..	..	..	..	+	..	..	+	..	+	..	..	..	
15	26	..	..	..	1	..	..	..	..	+	..	..	..	..	..	..	
16	28	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
17	29	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
18	30	..	..	..	..	+	..	+	..	..	..	..	1	..	..	..	
19	32	..	..	..	..	..	..	+	..	..	..	..	1	..	..	..	
20	34	..	..	+	..	..	..	..	+	..	..	1	..	..	..	..	
21	35	1	..	..	..	..	..	..	..	+	..	..	..	..	..	..	
22	36	..	..	..	..	..	..	..	..	+	+	..	1	+	..	..	(Hay-fever)
23	37	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
24	39	..	..	+	1	..	..	..	..	..	..	..	..	..	..	..	
25	40	..	..	+	..	..	..	..	..	..	..	1	..	..	..	..	
26	41	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
27	42	..	..	..	..	..	+	..	+	..	..	..	1	..	..	..	
28	43	1	..	..	..	..	..	..	..	+	..	..	..	..	..	..	
29	44	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
30	45	..	..	..	..	..	+	+	..	..	..	..	1	..	..	..	
31	46	..	..	..	..	..	..	+	..	..	..	+	+	..	..	1	Inanition
32	47	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
33	48	..	..	+	1	..	..	..	..	+	..	+	..	..	..	..	
34	49	..	..	..	..	..	..	..	+	..	+	..	1	..	..	..	
35	50	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
36	52	..	..	1	..	..	..	..	.	..	..	..	..	..	..	..	
37	53	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
38	54	..	..	..	..	..	+	..	..	+	+	..	1	+	..	..	
39	55	..	..	+	..	..	..	..	+	..	+	..	1	..	..	..	
40	56	..	1	..	..	..	..	..	..	..	..	..	..	+	..	..	
41	59	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
42	61	..	..	..	..	+	..	+	..	..	+	+	1	..	..	..	
43	62	..	..	..	..	..	..	+	..	..	..	..	1	..	..	..	(Aortic regurgitation)
44	63	..	..	.	..	+	..	..	+	..	..	..	1	..	..	..	
45	64	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
46	65	..	..	..	..	..	..	..	..	+	+	+	1	..	..	..	
47	66	..	..	..	..	+	+	..	+	..	+	+	1	..	..	..	
48	67	..	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
49	68	..	..	1	..	..	..	..	..	..	..	..	..	..	..	1	Dwarf
50	70	..	..	..	..	+	..	+	..	..	+	..	1	..	..	..	
51	71	..	..	..	..	+	..	..	+	..	..	..	1	..	..	..	
52	72	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
53	73	..	..	..	1	..	..	..	..	+	..	..	..	..	..	..	
54	74	..	..	..	..	..	..	..	..	..	..	1	..	..	..	..	
55	75	..	..	+	..	..	..	+	..	..	..	..	1	..	..	..	
56	76	..	..	..	..	+	..	..	..	+	+	..	1	..	..	..	
57	77	..	..	..	..	..	..	..	..	..	..	..	..	1	..	..	
58	78	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
59	79	..	..	+	..	+	..	+	..	..	..	..	..	..	..	1	Ulcer
60	80	..	..	..	..	..	..	..	..	..	..	+	+	..	1	..	
61	81	..	..	..	..	..	+	+	..	..	..	..	1	..	..	..	
62	82	..	..	..	..	..	..	+	..	..	..	+	1	..	..	..	
63	83	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
64	84	..	..	..	..	..	..	+	..	..	+	..	1	..	..	..	(Angioneurotic edema)
65	85	..	..	..	..	..	..	..	..	..	..	..	..	..	..	1	Elevated temperature (cause unknown)

TABLE 1.—*Classification of One Hundred So-Called Normal Men on the Basis of the Results of Physical Examinations—Continued*

						Cardiovascular Renal											
			Tuberculosis, Shown by Roentgenogram					Blood Pressure									
Serial Number	Individual Number	Normal Persons	Active	Healed	Syphilis	Arteriosclerosis of Large Vessels (X-Ray)	Myocarditis (X-Ray)	High	Normal	Low	Changes in Urine (Casts or Albumin)	Changes in Skin Capillaries	Cardiovascular Renal	Sensitized	Nervous	Miscellaneous	
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	
66	86	..	..	..	..	..	..	..	..	..	..	..	..	+	1	..	
67	87	1	..	..	..	..	..	..	..	+	..	..	..	..	..	..	
68	88	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	
69	89	..	..	1	..	..	..	..	..	+	..	..	..	..	..	..	
70	90	..	..	..	..	..	..	..	..	..	..	..	..	..	1	..	
71	91	..	..	..	+	..	..	..	+	..	..	+	1	..	..	..	
72	92	..	..	..	..	..	..	..	..	+	..	..	..	..	1	..	
73	93	..	..	..	..	..	+	..	+	..	..	..	1	+	..	..	
74	94	1	..	..	..	..	..	..	..	..	..	..	..	..	..	..	
75	95	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
76	96	..	..	..	..	+	..	+	..	..	..	..	1	..	..	..	
77	97	1	..	..	..	..	..	..	..	+	..	..	..	..	..	..	
78	98	..	..	..	..	+	..	..	+	..	..	..	1	..	..	..	
79	99	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
80	100	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
81	101	..	..	+	..	..	..	..	..	..	..	+	..	1	..	..	
82	102	..	1	..	..	..	..	..	..	..	..	..	..	..	..	..	
83	103	..	..	..	..	+	+	..	+	..	..	..	1	..	..	..	
84	104	..	1	..	..	+	..	+	..	..	..	..	+	..	..	..	
85	105	..	..	1	..	..	..	..	..	+	..	..	..	..	..	..	
86	106	..	..	..	..	+	..	..	+	..	..	..	1	..	..	..	
87	107	..	..	..	..	+	+	..	+	..	..	..	1	..	..	..	
88	108	..	1	..	..	..	..	..	..	+	..	+	+	..	..	..	
89	110	..	..	1	..	..	..	..	..	..	..	..	..	..	..	..	
90	111	..	..	+	..	+	..	..	+	..	..	..	1	..	..	..	
91	112	..	..	..	..	+	..	..	+	..	..	..	1	..	..	..	
92	113	..	..	+	..	+	..	..	+	..	..	..	1	..	..	..	
93	114	..	1	..	..	+	..	+	..	..	+	..	+	..	..	..	
94	115	..	..	+	..	..	..	+	..	..	+	..	1	..	..	..	
95	122	1	..	..	..	..	..	..	..	+	..	..	..	..	..	..	
96	127	..	..	+	..	..	..	..	..	+	+	..	1	..	..	..	
97	128	..	..	+	..	+	..	..	+	..	+	+	1	..	..	..	
98	129	..	1	..	..	..	..	..	..	..	+	+	+	..	..	..	
99	130	..	..	..	..	..	..	..	..	+	+	..	1	..	..	..	(Aneurysm)
100	134	..	..	..	..	+	..	+	..	..	+	..	1	..	..	..	
		20	9	17	4	..	..	..	..	..	..	3	37	2	4	4	

COMMENT

The Normal Group.—In the normal group, there have been included men whose blood pressure is under 140, with no urinary changes, no roentgen evidence of tuberculosis and no alterations of the capillaries of the skin, with negative Wassermann reactions and without history of sensitization.

Even with such criteria, it is to be expected that certain ones may be abnormal in the sense that chronic pathologic conditions of the organs, either anatomic or functional, may exist, but need not be clinically apparent in one examination. Thus, a number of deviations are observed in the course of the examinations.

Blister Time: The blister time is shortened only in patient 122, a young medical instructor, apparently normal, who gives a history of

TABLE 2.—*The Results of the Examinations of*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
														Systolic	Diastolic			
4	6	62	9.5	11.8	21.2	1.8	94.3	...	8.28	2	−12	0.34	...	114	90	80	21	45.5
122	4	68	17	10.6	19.2	1.81	50	1.8	8.06	?	− 7	0.37	2.4	102	50	68	− 3	− 6
29	6.5	70	10.7	10	23.9	2.39	76	1	8.28	3.25	+ 3.5	0.74	1.1	134	88	76	+24	+24
35	8	54	6.7	8.7	25.2	2.9	79	2	8.28	1.25	−12.3	0.38	2	108	78	62	−33	−47
41	6	55	9.1	9.8	21.2	2.16	70	1	8.49	1.25	+15	0.26	3.2	110	74	64	+26	+31
43	6.25	60	9.7	9.2	17.4	1.89	67	1	7.63	1.75	− 4.4	0.27	3.5	96	50	74	−18	−40
44	8	56	7	10	17.6	1.76	90	2	8.49	1.75	− 1.2	0.36	3	120	68	60	− 7	+22
50	8	71	8.8	11.4	27.4	2.4	..	2.3	8.28	3	+21	0.48	2	128	70	67	−12	−20
64	6.5	66	10	9	16.6	1.84	52	3.5	7.41	3	+23	0.22	5	113	59	64	−15	+18
72	6	69	11.5	10.8	18.7	1.73	72	2.8	7.73	2	+15.9	0.27	3.6	114	76	54	−25	+46
78	7	86	12	8.4	18.8	2.23	67	1.5	8.49	3.25	− 6.2	0.62	1	122	70	74	−11	+20
83	9	51	5.6	8.2	19	2.31	68	1.5	7.73	1.5	− 7	0.16	4	118	64	58	− 9.6	+ 9
87	6	56	9.3	8.4	19.5	2.32	94	2.3	7.55	1.5	+18	0.42	4	102	58	69	−40	−53
97	6	54	9	8.4	20.9	2.37	60	1.4	7.85	1.75	+25	0.22	4.5	100	63	68	−20	+30
17	8	66	8.2	12.7	18.2	1.43	61.5	5	8.72	1.5	−11	0.22	6	130	70	66	0	0
53	8	62	7.7	....	22.8	....	77	3	8.06	1.5	+31.8	0.35	6.7	125	73	80	+32	+32
59	6	52	8.6	9.6	18.8	1.95	85	5	7.85	1.5	− 6.5	0.16	4	116	69	74	− 2	− 8
8	7	75	10.7	10.5	21	2	73	2.12	8.06	1.15	− 8	....	2.2	120	86	64	−90	−120
37	9	56	6.2	10	22.6	2.26	75	1.4	7.85	1.5	−24	0.34	3	116	70	84	− 8	− 6
94	6	53	8.8	8.4	17.5	2.08	75	1.7	7.85	1.45	− 1.8	0.43	...	134	78	53	−20	+50
	6.8	62	9.3	9.7	20.3	2.1	72.8	2.22	8.04	1.83	+ 5	0.33	3.7	116	70	68	+19.6	+28.6

TABLE 3.—*The Results of the Examinations of the Men who Were*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
														Systolic	Diastolic			
95	6	59	9.8	7.8	18.8	2.41	77	2.3	8.5	1.85	+26	0.39	1.6	110	66	78	+ 9	+17
3	6.5	67	11.1	11.1	16.3	1.47	73.3	1.86	7.41	1.5	− 6.5	0.33	...	114	65	76	+ 8	+26
13	8	64	8	9.6	23.8	2.48	78	4	7.7	2.5	−22	0.89	2.7	132	84	72	24	37
15	9	68	7.5	12.1	18.8	1.55	70.4	4	7.95	1.5	− 4.9	0.19	6	128	68	60	+13	−20
23	6	67	11.1	13.1	28.6	2.19	85	....	7.87	1.75	+10.9	0.42	3	102	58	82	−25	+41
24	6	70	11.6	11.7	24.8	2.12	81	....	7.20	2	+ 1	0.19	2	110	58	78	−50	+62
52	8	61	7.6	10.4	20.9	2	66	4	7.85	1.5	+ 0.5	0.44	1	110	61	75	0	+ 4
100	6	53	9	9	21.5	2.38	72	1.2	7.85	1	− 1.6	0.11	3.8	128	58	76	− 8	−13
110	7.5	64	7.2	12.1	16.3	1.34	61	2.5	7.20	4	+48	0.60	2	114	60	86	− 4	− 4
68	7	78	11	8.8	17.1	1.94	68	2.3	8.66	1.5	+25.8	0.53	5	138	76	89	−31	+36
89	6	52	8.6	9.2	16.7	1.81	75	2	7.51	1.25	+25	0.16	1.6	100	60	73	0	+ 2
99	9	77	8.1	9.5	17.9	1.86	71	4	7.85	4.5	− 3	0.14	4.2	116	78	70	+12	−24
105	9	62	7	9	17.1	1.81	52	1.6	7.63	2.5	+31.6	0.09	...	108	70	82	+26	+26
18	8	70	8.7	14.5	21.2	1.46	70.2	1.8	8.30	3.25	+ 4.2	1.00	2	120	80	88	16	....
28	6	64	10.6	11	24.1	2.19	72	1.4	7.63	1.75	+24.5	0.08	4	118	76	65	−21	+32
10	6	64	13.3	10.1	24.6	2.4	74	2.12	8.70	2.5	−12	0.42	3.6	120	70	70	0	0
47	5	62	12.8	10.4	26.2	2.51	72	1.5	8.38	1.45	+34	0.13	5	136	64	70	− 5	+10
	7.3	64.8	9.6	10.5	20.8	1.98	71.6	2.43	7.88	2.15	+ 8	0.36	2.97	117	67	75	13.4	20

the Men Who Were Grouped as "Normal"

CO_2 Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
64	Sthenic	—	+	Normal	..	40	237	...	22.8	10.6	16	17	10.2	0	10.2	0
56.8	Asthenic	..	..	Normal	5	33	189	209	20	7.8	10	6.6	12	9	21.2	0
60.1	Sthenic	..	+	Normal	15	43	214	...	26.8	9.4	14	12.2	7.2	0	5	0
57.6	Sthenic	..	+	Normal	20	44	203	...	22.8	11	14.8	20.4	9.2	0	5.2	0
58.6	Asthenic	..	0	Normal	7	40	216	...	24	7.2	13.8	18.8	6.2	0	5.8	0
60.1	Asthenic	..	0	? Decreased in quantity	7	45	231	...	22	7.4	11.2	20.6	10	0	11	0
57.1	Sthenic	..	0	Normal	20	48	244	...	19.6	9.4	12.8	15	10.2	3.8	15	4.4
64.9	.....	..	..	Normal	15	20	237	...	24.8	10.6	9.8	15.4	10.4	10	14	0
55	Sthenic	..	..	Normal	7	31	208	180	20	10.6	13	15	12.2	10.8	16.2	0
60.6	Sthenic	..	+	Normal	20	42	230	185	18	12.2	15.6	17.8	15.4	6.6	20.2	15.4
62.6	Asthenic	..	..	Normal	10	33	203	238	19.6	12	9.4	20.4	12.4	6.2	20.2	10
53.1	Sthenic	..	..	Normal	20	43	258	196	17.2	9.2	9.2	20.8	13.4	11	21.4	7.4
55.4	Sthenic	..	..	Normal	18	46	200	222	16	8.8	10	12.4	12	5.4	25.4	10.2
57.2	Sthenic	..	+	Slight dilatation	20	53	230	245	19.2	9	8.8	16.4	12	9	33	0
59.1	Normal	..	0	Normal	20	28	216	...	22.8	10.2	12.4	7	20.6	10.4	30.4	2.6
53.9	Sthenic	—	..	Normal	10	39	231	...	17.2	11.8	10.4	26.4	12.2	11.2	23	6
56.6	Sthenic	—	..	Normal	10	37	252	...	23.6	7.2	9.2	21.4	15.6	8	23.4	6
56.1	Asthenic	—	+	.....	17	38	200	...	20.4	9.8	13.2	13.4	14.4	0	19	0
52	Sthenic	..	+	Normal	20	45	254	...	22.8	7	10.2	15.2	6	0	8.4	0
51.5	Sthenic	—	..	Normal	15	57	236	303	20	6	11.2	14	11.2	7.8	30.6	0
57.6					14.5	40.2	224	222	21	9.36	11.7	16.3	11.6	5.45	17.9	3

Grouped as Having Roentgenographic Evidence of Healed Tuberculosis

CO_2 Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
61.6	Sthenic	Healed	..	Normal	10	54	222	318	23.6	6.4	10.2	12.6	12	6.2	26.2	..
....	.....	Healed	+	Normal	14	25	224	243	19.4	12.2	12.4	18.2	6.4	....	4.8	..
68.6	Asthenic	Healed	+	Normal	15	53	223	185	13.2	6.8	12.4	11.2	22.6	9.2	25.6	..
67.6	Sthenic	Healed	+	.....	38	60	210	...	23.2	12.6	11.2	12.4	11.6	12	12.4	10
57.4	Sthenic	Healed	0	Normal	28	54	233	...	17.2	8.2	10.6	17.8	9.2	3.2	7.2	4
53.7	Sthenic	Healed	+	Normal	20	30	219	...	16.8	12	9	27.2	6.6	....	7.2	..
52.9	Sthenic	Healed	..	Normal	15	36	213	...	17.6	10	12.8	19.2	11.2	12.4	20	7.8
58.3	Sthenic	Healed	..	Normal	5	45	241	208	18.8	8.6	11.4	10.6	12	9.2	27.6	..
57.2	Asthenic	Healed	..	Decreased	30	62	190	222	21.8	4.2	9.6	14.6	12	9.4	18.2	..
51.1	Asthenic	Healed	..	Normal	10	35	217	238	18	9.6	12.4	10.2	12	11	22.4	1
56.3	Asthenic	Healed	..	Normal	16	41	204	222	20.8	9.8	9.2	20	10.2	....	20.4	..
57.4	Sthenic	Healed	..	Normal	11	46	228	230	20.4	7	12.2	11.2	12.2	9.2	29.4	..
64.4	Asthenic	Healed	?	Normal	15	56	194	238	19.6	5.6	9.2	16	12	10.4	27.2	..
58.4	Asthenic	Healed	0	Normal	10	31	200	...	....	....	6.6	22.6	....	....	....	..
66	Asthenic	Healed	+	Normal	25	43	200	...	20	12.2	10.8	15.2	7.4	....	7.2	..
60.4	Sthenic	Healed	0	Normal	7	40	230	...	20	8.4	12.6	14.6	9	7.2	12.2	..
56.4	Sthenic	Healed	+	Normal	15	38	260	...	22.6	5.2	14.2	10.8	9	6	....	..
57.9					16.5	43.6	218	233	19.2	8.66	11	15.5	11	6.2	17	1.5

TABLE 4.—*The Results of the Examinations of the Men Grouped*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
															Systolic	Diastolic			
20	6	64	10.6	11.4	17.4	1.53	85	1.70	8.28	1.5	+20.4	0.25	5	..	130	76	80	+13	+28
25	6	57	9.5	11.1	28.8	2.60	67	0.43	8.50	1.75	+ 2	0.24	1.2	+	140	80	86	+35	+44
56	6	61	10	9.8	28.6	2.52	65	1.8	9.13	2.15	+17.9	0.32	1	..	124	88	79	+14	+22
104	9	54	6	7.4	22.9	3.09	55	1.2	7.51	1.75	+27.5	0.08	1.2	..	176	100	84	+11	+11
114	8.5	64	6	8	19.2	2.4	75	2.3	8.06	2.25	+11.2	0.12	4	Albumin, blood	174	60	48	+ 6	−60
129	15	52	3.5	8.9	19	2.13	83	1.3	7.85	2.5	+28	0.22	2.2	+	116	66	92	10	13
108	8	63	8	10.4	15.3	1.47	63	1	7.85	1.75	+17	0.44	0.6	..	94	52	71	+ 9	−29
102	11	64	5.8	10.6	17.3	1.63	62	0.82	7.95	1.5	+22	0.20	2.4	..	114	60	96	+11	+ 5
88	7.25	58	8	9.4	13.1	1.4	79	2	7.63	2	.....	0.68	2.5	..	128	76	76	−10	0
	8.4	59	7.5	9.6	20.1	2.08	70	1.4	8.08	1.9	18.2	0.28	2.2		133	73	78	+11	+23

TABLE 5.—*The Results of the Examinations of the Men in the Cardiovascular*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure			Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
														Systolic	Diastolic	Pulse Rate		
46	6	59	10	13.8	17.4	1.24	61	2.3	7.63	1.15	+13	1.7	2	140	82	76	+15	+37
21	7	62	9	10.2	25.6	2.51	72	4	8.06	1.75	+ 4.3	0.74	3.9	140	80	72	0	− 8
32	6	60	10	9.5	26.1	2.75	76	2.3	8.80	1.75	+22	1.18	7.4	144	86	74	+22	+30
45	6	54	9	11.2	16.6	1.48	77	1.5	7.73	0.75	+20	0.28	7.4	162	114	84	− 3	− 8
79	15	86	5.7	11.2	20	1.78	67	1	8.78	4	−15.2	0.71	7.7	140	80	60	+ 8	+10
81	6	59	10	8.4	25.8	3.07	63	1.7	8.49	1.5	+35	0.10	2.3	144	54	76	+ 4	+ 4
75	9	60	6.6	10.8	19.2	1.78	75	1.6	9.23	3	+ 2.5	1.3	5	146	80	77	− 9	−15
82	6	58	9.6	11.4	17.2	1.5	58	2	7.41	1.5	+ 7	0.20	5.7	170	100	61	+31	−37
30	6	55	9.1	10.3	24	2.33	76	....	7.07	1.5	− 5.9	1.05	1.8	150	72	85	0	−10
96	8.25	57	7	8.2	17	2.02	77	1.8	7.26	1.75	+31	0.11	2.6	140	85	68	+25	−28
	7.5	61	8.6	10.47	20.8	2	70.2	1.82	8.04	1.86	11.4	0.7	4.6	147	83	73	9.3	14.1

as Having Roentgenographic Evidence of Active Tuberculosis

CO_2 Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
62.3	..	Asthenic	+++	0	Normal	10-20	42	226	...	24.2	6.6	12.4	15.4	10	2.6	9	0
59.8	..	Asthenic	+++	0	Normal	20	35	183	...	21.4	12.2	8.2	17.8	9	15.2	10	6.2
56.5	..	Sthenic	+++	..	Normal	15	44	247	...	17.2	5.8	10.8	22.4	14	7	21.4	7.2
57.2	+	Dilatation of aorta, arteriosclerosis	+++	..	Normal	25	76	235	230	20.8	6.2	10.8	10	12	0	15.2	0
60.6	..	Sthenic	Left upper bronchus +	+	Normal	25	79	235	208	20	7.2	10.2	10.2	12	9	22.2	0
61.1	..	Sthenic	+	+	Granulations	17	66	247	238	18.4	7	10.6	9.6	12.2	0	13.2	0
54.1	..	Asthenic	Hilum bronchi	..	Slight granulations	18	67	196	139	18	2.4	10.2	11	14.8	13.2	28.4	3.4
60.9	+	Asthenic	+	+	Normal	40	65	170	208	23.2	7.4	10.8	15	12.2	0	18.2	7
58.1	..	Asthenic	+++	..	Normal	15	55	203	230	18.4	11	11.6	20	12.4	12	27.6	0
58.8						21	58.7	215	208	20	7.2	10.6	14.6	12	6.4	18	2.6

Renal Group Having Increased Blood Pressure but No Urinary Changes

CO_2 Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
56.2	..	Asthenic	..	+	Sluggish, empty	15	29	168	...	21.2	13.2	15.0	16.2	12.2	11.2	25.2	9.2
62.9	..	Asthenic	Healed	0	Dilated, in granulations	25	56	200	...	23.2	12.6	8.8	13.2	7.2	2.6	5.2	...
54.1	..	Sthenic	..	0	Normal	25	26	190	...	23.6	11.2	11	21.4	9.8	....	8.4	...
54.3	..	Sthenic, myocarditis	..	0	Normal	20	40	317	...	20.4	9.8	14.2	21.4	16.4	12	20	4.8
57	+	Arterio-sclerosis	Healed	..	Normal	20	58	220	230	19.2	9.4	10.2	17.8	8.2	12.2	30.6	5
57	..	Myocarditis	..	+	Normal	45	68	209	222	14	6.2	10.2	15	10	....	16.4	9.6
61.6	..	Sthenic	Healed	+	Normal	10	54	243	278	20.4	10.2	18	15.2	10	....	23.4	8
58.8	..	Sthenic	..	1890	Slightly tortuous	25	66	208	190	21.2	7	14.2	14.2	11	....	27.6	9
62	+	Arterio-sclerosis	..	0	Normal	15	42	175	...	20	8.8	8.2	16	7.2	....	7.2	...
53.4	..	Arterio-sclerosis	..	+	Normal	40	70	245	167	18	8.2	11.4	15.4	12.4	....	28.4	...
57.7						24	50.9	217.5	217	20.1	9.72	12	16.6	10.4	3.8	19.2	4.6

TABLE 6.—*The Results of the Examinations of the Men in the Cardiovascular*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
															Systolic	Diastolic			
61	6	10	11.6	7.6	17.9	2.35	72	3.5	7.41	1.75	+ 0.9	0.28	7.4	+	142	82	64	+ 8	+17
70	10.5	74	7	11.4	16.6	1.45	67	1.9	8.65	1.25	+23	0.39	4	++	148	50	76	— 6	+ 2
84	11	71	6.4	10	17.8	1.78	67	1	7.85	1.5	— 5	0.28	2.8	+	140	78	80	+ 6	+ 3
115	8	46	5.7	7.8	15.2	1.95	60	0.66	8.28	1.65	+15	0.28	2	Albumin, sugar +	148	84	84	— 4	— 4
134	15	60	4	9.9	15.4	1.56	71	1.4	7.85	1.35	— 4	0.7	...	Casts	146	86	78	0	+ 5
	10.1	64	7	9.34	16.6	1.82	67	1.7	8	1.5	6	0.38	4		145	76	76	0	+ 4.6

TABLE 7.—*The Results of the Examination of the Men in the Cardiovascular Renal Group with Normal*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
														Systolic	Diastolic			
42	7.25	47	6.5	11.4	17.8	1.56	71	1	7.63	2	+ 6.8	0.15	4.5	136	70	86	0	+19
113	6.5	60	9.2	10.2	18.6	1.82	66	1.5	7.41	1.75	— 6.2	0.34	2.2	136	72	60	+ 8	+ 8
71	6	70	11.6	8.8	17.5	2	73	2.3	8.5	1.1	+ 7.4	0.36	1.4	114	70	88	+18	+18
93	6	50	8.3	7.6	24.5	3.2	70	1.4	8.59	1.45	0	0.25	2.4	114	71	86	+19	+19
103	6	52	8.6	9.2	17.3	1.88	57	1.5	7.73	1.75	+ 2	0.39	1.4	126	70	76	— 1	+ 6
106	6	71	12	11.2	19	1.69	65	1.7	8.06	1.45	— 6	0.63	2.2	120	80	84	— 5	— 1
107	9	58	6.4	8	18.4	2.3	60	1.5	8.06	4.75	— 6.5	0.33	2.8	134	72	72	— 1	+ 2
111	6	57	9.5	11.8	18.3	1.5	75	1.5	8.28	1.15	+31	0.33	1.2	122	70	92	+19	+21
112	6	54	9	12.6	18	1.42	68	2.1	7.44	1.15	+19.6	2.7	2.4	139	80	75	+ 5	+14
98	8.25	57	7	8.2	17	2.07	77	1.85	7.41	1.75	+31	0.11	2.6	140	85	68	+25	+28
91	7	56	8	....	....	....	67	2	7.85	2.5	— 1.7	0.30	4	136	64	76	+26	+34
63	7.5	71	9.4	11.4	20.9	1.82	62	1.5	7.63	5	+ 0.65	1.4	5	116	62	60	+ 5	+35
	6.8	58.5	8.7	10	18.6	1.86	67	1.65	7.90	2.15	6.5	0.60	2.67	127	72	77	+ 9.8	17

Renal Group Having Increased Blood Pressure with Urinary Changes

CO_2 Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
53.1	..	Arteriosclerosis	..	..	Slight granulation	7	51	208	267	19.6	9	14.4	17.6	13.4	0	20.2	5
56	+	Arteriosclerosis, dilated aorta	..	..	Normal	45	65	264	222	18	11	9.8	18.2	10	0	24.6	6.6
53.1	..	Asthenic	..	+	Normal	20	73	200	167	16.4	8.4	8.2	19.2	10.2	7.2	20.6	0
51.8	..	Sthenic	Healed	..	Normal	10	66	215	247	18.2	6.2	11	13.2	14.2	8	16	9.6
54.8	..	Arteriosclerosis	..	+	Normal	12	67	233	196	23.6	17.8	11.4	13.2	19.2	9.6	28.6	3.2
53.7						19	64.5	224	220	19	8.9	11	16.4	13.4	5	22	5

Blood Pressure and Normal Urine but with X-Ray Evidence of Arteriosclerosis or Myocarditis

CO_2 Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
54.5	..	Myocarditis	..	0	Normal	32	33	241	...	19.2	11.8	10.8	16.8	9.2	4.6	6.8	0
62.7	++	Arteriosclerosis	Healed	..	Normal	12	59	213	222	18.4	9.2	9.6	18.8	10.8	10.6	18.2	0
57.9	..	Arteriosclerosis	..	..	Normal	15	42	195	256	19.2	9.6	12.6	18.2	15.4	11	24.4	8.2
57	++	Myocarditis	..	..	Normal	12	53	267	230	20.4	8.6	12.4	15	10	0	22.4	0
55.3	+	Arteriosclerosis, myocarditis	..	..	Normal	5	59	270	215	22.4	9	12.2	18.2	12.2	0	18.2	0
49.5	+	Aorta, arterio-sclerosis	..	..	Normal	30	60	243	222	19.6	7	9.2	14.4	11.2	0	25.6	0
55.2	+	Myocarditis	..	+	Normal	15	62	265	256	20.8	5.8	8.6	11.2	13.4	6.2	21.4	0
55.3	++	Arteriosclerosis	++	++	Normal	15	60	200	290	22	9.4	11	15	10.8	5.6	26.2	0
59	..	Arteriosclerosis	+	+	Normal	18	60	218	215	22.4	7.2	10.8	18.4	9.6	0	24	0
53.4	..	Arteriosclerosis	..	+	Normal	40	70	245	167	18	8.2	11.4	15.2	12.4	0	28.4	0
58.9	+	Arteriosclerosis	..	..	Venous capillaries tortuous	45	66	208	222	16.8	6.8	8.8	16.6	12	9.4	22	0
62.4	..	Arteriosclerosis	Healed	..	.....	17	40	190	215	20	11	17.2	15.2	12.2	0	26.2	0
55.9						21	55.3	229	228	20	8.62	11.2	16.1	11.6	4	21.8	0.68

TABLE 8.—*The Results of the Examinations of the Men in the Cardiovascular*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
															Systolic	Diastolic			
14	7	74	10.5	11.2	19.6	1.75	67	1.7	8.06	1.55	— 2.7	0.20	2.1	Casts, sugar	128	80	76	0	0
55	8.5	60	7	8	24.9	3.1	73	1.5	7.75	2.75	+ 6.2	0.38	0.6	+	128	68	84	+ 5	+ 8
66	6	78	13	11	20	1.82	67	1.22	8.66	0.85	+ 1.3	0.37	3.5	+	128	66	77	+37	+44
128	15	68	3.8	9.4	19.7	2.09	79	0.8	8.06	4	—18	1	0.6	+++	122	80	84	+13	+24
49	6	66	11	11	25.2	2.29	74	4.8	8.28	5.5	+ 7.2	0.32	2	+	134	72	60	+21	+41
	8.5	67	9	10.1	21.9	2.2	72	1.14	8.16	2.93	0	0.45	1.76		128	73	76	+15	+23

TABLE 9.—*The Results of the Examinations of the Men in the Cardiovascular Renal Group and Those with Roentgenographic*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Wassermann Reaction	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure		Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
															Systolic	Diastolic			
26	6.5	72	11	10.2	26.6	2.61	69	1.9	8.28	Slight	2.25	+ 9.6	0.28	2	92	48	68	+12	+ 6
48	6.75	66	9.7	9.6	27.6	2.87	71	1.5	8.59	Slight	1.25	+ 8.5	0.10	1.6	104	72	84	+ 9	+12
73	9	69	7.6	11.2	19.5	1.74	71	2.3	8.5	Slight	2.1	+16.3	0.20	3	104	70	54	+ 3	+10
23	6	67	11.1	13.1	28.6	2.19	85	...	7.87	..	1.75	+10.9	0.42	3	102	58	82	+25	+41
89	6	52	8.6	9.21	16.7	1.81	75	2	7.51	..	1.25	+25	0.16	1.6	100	60	73	0	+ 2
105	9	62	7	9	17.1	1.81	52	1.6	7.63	..	2.5	+31.6	0.09	...	108	70	82	+26	+26
87	6	56	9.3	8.4	19.5	2.32	94	2.3	7.55	..	1.5	+18	0.42	4	102	58	69	+40	+53
97	6	54	9	8.4	20.9	2.37	60	1.4	7.85	..	1.75	+29	0.22	4.5	100	63	68	+20	+30
122	4	68	17	10.6	19.2	1.81	50	1.8	8.06	..	?	— 7	0.37	2.4	102	50	68	— 3	— 6
43	6.25	60	9.7	9.2	17.4	1.89	67	1	7.63	..	1.75	— 4.4	0.27	3.5	96	50	74	+18	+40
35	8	54	6.7	8.7	25.2	2.9	79	2	8.28	..	1.25	+12.3	0.38	2	108	78	62	+33	+47
	6.7	61	9.3	9	19.8	2.2	70.8	1.78	8		1.73	+13	0.26	2.76	101	61	71	+16	+23

Renal Group Having Normal Blood Pressure with Changes in the Urine

CO_2 Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
65	..	Asthenic	0	0	Normal	40	36	198	278	24.4	6.2	13.2	7.2	15	4.4	9.8	10
56.6	..	Asthenic	Healed	+	Normal	20	50	170	...	17.6	8.2	10.2	19.6	11.2	....	12.2	..
53.1	+	Arteriosclerosis, myocarditis	..	—?	Tortuous, beaded	30	64	257	215	20	9.2	13.6	16.6	10.2	....	18.2	..
58.1	..	Arteriosclerosis	Healed	..	Slight granulation	24	66	180	230	....	....	12.6	10.2	14.4	....	22.6	..
59.1	..	Sthenic	..	..	Normal	15	42	239	...	18.4	10.2	13	12.2	4.2	1	9	..
58.4						26	51.6	209	241	20	8.2	12.4	12.6	11	1	14.4	2

with Blood Pressure Under 110 (Including the Syphilitic Group, the Normal Group, Evidence of Healed Tuberculosis)

CO_2 Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
63.4	Sthenic	..	0	Normal	35	30	210	...	19.6	10	10	8.6	7.2	6.4	10.4	0
58	Sthenic	Healed	0	Tortuous	35	46	222	...	19.2	8.4	15.2	12	8	0	7	0
59.7	Asthenic	..	..	Normal	35	48	191	247	17.6	8.2	12	16	15.6	0	2	8
57.9	Sthenic	Healed	0	Normal	28	54	233	...	17.2	8.2	10.6	17.2	9.2	3.2	7.2	6
56.3	Asthenic	Healed	+	Normal	16	41	204	222	20.8	9.6	9.2	20	10.2	0	20.4	0
64.4	Asthenic	Healed	?	Normal	15	56	194	238	19.6	5.6	9.2	16	12	10.4	27.2	0
55.4	Sthenic	..	..	Normal	18	46	200	222	16	8.8	10	12.4	12	5.4	25.4	10.2
57.2	Sthenic	..	+	Dilated, U-shaped	20	53	230	245	18.2	9	9.8	16.4	12	9	32.6	0
56.8	Asthenic	..	..	Normal	5	33	189	209	20	7.8	10	6.6	12	9	21.2	0
60.1	Asthenic	..	..	Decreased	7	45	231	...	22	7.5	11.2	20.6	10	0	11	0
57.6	Sthenic	..	+	Normal	20	44	203	...	22.8	11	14.8	20.4	9.2	0	5.2	0
58.7					21	45.1	209	230	19.44	8.5	11	15.2	10.6	3.94	14.2	2

TABLE 10.—*The Results of the Examinations of the Men in the Cardiovascular*

Individual Number	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure: Systolic	Blood Pressure: Diastolic	Pulse Rate	Epinephrine, Pulse Pressure, per Cent	Epinephrine, Pulse Pressure × Pulse Rate, per Cent
36	8	58	7.2	12.1	26.3	2.17	90	2	8.28	2	+ 1.3	0.11	3.8	+	104	50	84	+22	+28
130	15	71	4.7	9.5	15.5	1.63	86	0.66	7.99	2	+12	0.35	...	+++	106	..	64	....	....
54	6	60	10	....	22	....	80	2	8.28	1.25	— 3.4	0.26	2.6	+	104	80	68	+66	+90
65	6	61	10	9.8	16.4	1.67	65	1.7	8.28	3	+29	0.85	0.4	++	100	70	63	+30	+42
76	8.5	76	9	10.8	20.2	1.87	77	2.3	8.2	1.65	+ 8	0.28	9.6	+	108	82	67	+11	+ 8
127	13	50	3.8	9.7	16.2	1.67	81	2	7.85	4.25	— 3.5	1.2	3	+++	108	74	88	+60	+54
	9.7	59	7.4	10.4	19.4	1.86	80	1.77	8.14	2.36	7.2	0.51	3.9		105	71	72	+38	+44

TABLE 11.—*Averages of the Results of the Individual*

	Number in Group	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Protein, Mg.	Wassermann Reaction	Kromayer Light Erythema Time, Hr.	Basal Metabolic Rate	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure: Systolic	Blood Pressure: Diastolic	Pulse Rate	Epinephrine, Pulse Pressure, per Cent
Table 2: Normal group.....	20	6.8	62	9.3	9.7	20.3	2.1	72.8	2.22	8.04	....	1.83	+ 5	0.33	3.7	...	116	70	68	+19.6
Table 3: Normal group with x-ray evidence of healed tuberculosis	17	7.3	64.8	9.6	10.5	20.8	1.98	71.6	2.43	7.88	....	2.15	+ 8	0.36	3	...	117	67	75	13.4
Tables 2 and 3: Average normal group	37	7	63.3	9.4	10.1	20.6	2.04	72.3	2.32	7.96	....	1.97	+ 6.3	0.35	3.5	...	116	69	71	+16.5
Table 4: Roentgenographic evidence of active tuberculosis.	9	8.4	59	7.5	9.6	20.1	2.08	70	1.4	8.08	....	1.9	+18.2	0.28	2.2	3/9	133	73	78	+11
Table 5: Increased blood pressure; urine normal.....	10	7.5	61	8.6	10.47	20.8	2	70	1.82	8.04	....	1.86	+11.4	0.7	4.6	0	147	83	73	+ 9.3
Table 6: Increased blood pressure; urine + ...	5	10.1	64	6.4	9.34	16.6	1.82	67	1.7	8	....	1.5	+ 6	0.38	4	5/5	145	76	76	0
Table 7: Normal blood pressure; normal urine; x-ray evidence of arteriosclerosis or myocarditis	12	6.8	58.5	8.7	10	18.6	1.86	67	1.65	7.90	....	2.15	+ 6.5	0.60	2.67	0	127	72	77	+ 9.8
Table 8: Normal blood pressure; urine +; arteriosclerosis or myocarditis.....	5	8.5	67	9	10.1	21.9	2.2	72	1.14	8.16	....	2.93	0	0.45	1.76	5/5	128	73	76	+15
Table 9: Low blood pressure; normal urine	11	6.7	61	9.3	9	19.8	2.2	70.8	1.78	8	3/11	1.73	+13	0.26	2.76	0	101	61	71	+16
Table 10: Low blood pressure; urine + ...	6	9.7	59	7.4	10.4	19.4	1.86	80	1.77	8.14	....	2.36	+ 7.2	0.51	3.9	6/6	105	71	72	+38

Renal Group Having Low Blood Pressure, with Changes in the Urine

CO_2 Combining Power	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
57.6	Asthenic	..	0	Normal	20	43	222	...	20.8	14.2	11.2	18	7.4	0	7.4	0
55.5	Aneurysm. sthenic	..	..	Normal	15	65	196	196	20	5.4	10.8	12.6	11.2	0	22.6	0
56.6	Myocarditic cirrhosis of liver, sthenic	..	..	Normal	25	49	256	... 185	21.2 14.8	10.4 13	11 12	18 19.8	12 9.2	0 10.2	11.0 10.4	0 0
53.1	Sthenic	..	..	Tortuous	12	34	221									
57.9	Arteriosclerosis, dilated aorta	..	..	Normal	10	43	230	215	20	6.6	12.4	19.6	11	7	12	0
59.1	Asthenic	Healed	..	Normal	16	65	180	247	18.4	9.4	12	10.2	15.4	12	22	0
56.6					16	49.8	218	211	19.2	9.8	11.8	16.4	11	4.8	14.2	0

Examinations Set Forth in Tables 2 to 10

Epinephrine, Pulse Pressure × Pulse Rate, per Cent	CO_2 Combining Power	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)	Clinical Diagnosis and X-Ray Diagnosis
+28.6	57.6	.....	7/20	....	14.5	40.2	224	222	21	9.36	11.7	16.3	11.6	5.45	17.9	3.1	
20	58.5	Healed parenchymal	6/17	....	16.5	43.6	218	233	19.2	8.66	11	15.5	11	6.2	17	1.5	Healed parenchymal tuberculosis
+24	58	.....	13/37	....	15.6	41.8	221	228	20	9	11.3	16	11.3	5.8	17.4	2.38	
+23	58.8	Active (roentgenogram)	3/ 9	2/ 7	21	58.7	215	208	20	7.2	10.6	15.6	12	6.4	18	2.6	Active parenchymal tuberculosis
+14.1	57.7	.....	2/10	3/10	24	50.9	217	217	20.1	9.7	12	16.6	10.4	3.8	19.2	4.6	Arteriosclerosis or myocarditis (5/10 x-ray)
+ 4	53.7	.....	2/ 5	1/ 5	19	64.5	224	220	19	8.9	11	16.4	13.4	5	22	5	Arteriosclerosis or dilated aorta (3/5 x-ray)
+17	55.9	.....	4/12	1/12	21	55.3	229	228	20	8.62	11.2	16.1	11.6	4	21.8	0.68	Arteriosclerosis or myocarditis
+23	58.4	.....	1/ 5	2/ 5	26	51.6	209	241	20	8.2	12.4	12.6	11	1	14.4	2	Arteriosclerosis
+23	58.7	.....	3/11	1/11	21	45.1	209	230	19.5	8.5	11	15.2	10.6	3.94	14.2	2	
+44	56.6	.....	....	1/ 6	16	49.8	218	211	19.2	9.8	11.8	16.4	11	4.8	14.2	0	

feeling tired. The blood sugar level and the blood pressure are low, the reaction to epinephrine is vagotonic and the weight/length ratio is low.

Permeability of the Capillaries: High permeability occurs in only one man (no. 78). The history is negative other than that the man has recently had an acute attack of rheumatism.

K/Ca Ratio: A low ratio (1.43) is found in patient 17, a young laboratory technician. He has a markedly vagotonic reaction to epinephrine and shows other abnormalities. A high ratio occurs in patient 35, who is apparently normal.

Kromayer Lamp Erythema Time: Two persons (nos. 29 and 78) have prolonged Kromayer light erythema time. These men have high resistance of the skin to electric current and increased muscular irritability, as well.[1]

The averages for this group of selected normal men, as compared with the averages for the entire series of 100, differ in the rapidity of the responses to cantharides, to Kromayer light and to ice, and in the lower resistance of the skin to electric current, and lower systolic blood pressure and pulse rate and the more marked reaction to epinephrine. The men are somewhat younger. Of the reactions to pharmacologic substances the wheal due to epinephrine is increased.

Healed Tuberculosis.—The group of men with roentgenologic evidence of healed parenchymal tuberculosis are slightly older. The group averages slightly higher in cholesterol, and somewhat lower in serum proteins. The Kromayer light erythema time is increased twenty minutes. The muscle irritability seems somewhat greater than for the normal group. The pulse rate is increased. The men are somewhat thinner. The intracutaneous skin reactions other than the reduction of the wheal and flare due to epinephrine show no marked deviations.

Active Tuberculosis.—When we turn to the group of men with x-ray evidence of active parenchymal lesions, several important differences make their appearance. It is probable that some of the differences are due to the increased age of the group and the associated cardiovascular renal disturbances. It should be emphasized that these men are ordinary workmen and there was no particular reason to suspect activity. The majority of the cases are undoubtedly chronic in a marked degree.

It will be noted that the blister time is longer, the permeability of the capillaries is low and, consequently, the inflammatory index is low,

1. Despite inclusion in this true "normal" group, we are inclined to consider patients 17, 29, 78 and 122 as abnormal because of their repeated deviations from apparently normal ranges for many of the tests. It was later found that patient 29 had bile in the urine.

and that the basal metabolic rate is distinctly increased, as are the muscle reactivity, the pulse rate and the ice reaction time. On closer examination (the section on the K/Ca ratio may be consulted here), it will be observed that the men can be grouped on the basis of the K/Ca ratio into those with low ratios and those with high ratios. Those with high ratios include the men with cardiovascular disturbances. Roentgenologic examination indicates that those with low ratios have asthenic hearts (all with low or normal blood pressure). Those with high ratios have sthenic hearts. Those with low K/Ca ratios have shorter reactions to the Kromayer light, lower blood pressure, lessened muscular irritability and diminished weight.

Cardiovascular Renal Groups.—If we average the cardiovascular renal group and compare it with the normal, it will be noted that the blister time is longer, the globulins considerably increased, the Kromayer light erythema time prolonged, the resistance of the skin increased, the CO_2 combining power diminished and the ice reaction prolonged. Some of these differences must, of course, be attributed to the advanced age of the men. If we contrast the men having positive urinary conditions in the cardiovascular renal group with those having no urinary changes, we find that the blister time is longer and the capillaries appear to be somewhat more permeable. There is more globulin and the resistance of the skin to electric current is lowered.

If we compare the groups having increased blood pressure (5 and 6) with the groups having normal blood pressure (7 and 8), the following differences make their appearance: The blister time in the groups with increased blood pressure is prolonged, the Kromayer lamp erythema time shortened, the basal metabolic rate heightened, the muscular irritability lessened and the vascular reaction to epinephrine diminished.

III. DETAILED STUDY OF THE "NORMAL" GROUP AND OF MISCELLANEOUS CLINICAL PATIENTS

In this article we present the results of the clinical response to each of the various tests that we have carried out. The material consists of the 100 so-called normal men, as well as a considerable number of persons with diseases, chiefly exophthalmic goiter, glaucoma, diseases of the skin and certain vascular diseases (Raynaud's, Buerger's, etc.).

In table 1, the identification number, age, sex, occupation, nationality and clinical diagnosis of each person are presented. The identification numbers marked with an asterisk indicate persons included in the group of 100 so-called normal men.

METHOD OF PRESENTATION OF RESULTS

Since many different tests were made on each person, we proceeded to study each reaction separately, and to permit a rapid survey of the results, we adopted the following method: Results of each test for the entire group were arranged in numerical progression. A chart was made of this curve, and at the bottom of the chart we indicated the location on the curve and the clinical classification of the individuals of the group of 100 "normal" men. At the top of each chart, we usually indicated the location and clinical classification of the patients, particularly those with exophthalmic goiter and those with glaucoma. In addition to this chart, we made a tabulation of the twenty persons at each of the extreme ends of the curve and endeavored to correlate the results of other tests with the results of the one under consideration.

As the charts were all prepared in a uniform manner the first one—the chart of the blister time—is explained in some detail.

BLISTER TIME

When one analyzes chart 1, a number of features immediately present themselves. There appear to be proportionately more persons with roentgenologic evidence of healed tuberculosis in the region of the prolonged blister time with the cantharides method. The persons with roentgenologic evidence of active tuberculosis also tend to have a longer blister time. There are more of the persons showing cardiovascular renal changes in this end of the curve. This seems to apply not only to the group with urinary changes but to those with changes in the capillaries of the skin. Advancing age, increasing blister time and more frequent cardiovascular renal injury are obviously associated The patients with glaucoma, as might be anticipated, are at the end of

TABLE 1.—*General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation*

Individual No.	Sex	Age	Nationality	Occupation	Clinical Notes
1	M	23	Jewish	Student	Out of school because of "nervous breakdown"
2	M	13	American	Schoolboy	Epilepsy and vasoneurosis
3*	M	25	Jewish	Instructor	Nervous; healed tuberculosis; father has Raynaud's disease
4*	M	40	American	Instructor	Normal
5	F	48	Jewish	Housewife	Nervous; cardiovascular renal condition; healed tuberculosis
6	M	49	Jewish	Painter	Arteriosclerosis and myocarditis; syphilis; died
7	M	25	American	Student	Gastric ulcer; mother died of exophthalmic goiter
8*	M	38	German	Instructor	Normal
9	M	27	American	.....	Exophthalmic goiter
10*	M	40	Norwegian	Technician	Healed tuberculosis
11	M	46	German	.....	Exophthalmic goiter
12	M	40	Bohemian	Painter	Traumatic atrophy of muscle
13*	M	53	American	Janitor	Healed tuberculosis
14*	M	36	German	Technician	Probably gallbladder disease; cardiovascular renal condition
15*	M	60	American	Technician	Healed tuberculosis
16	M	33	American	.....	Exophthalmic goiter
17*	M	28	German	Student	Normal, but with marked deviations in many tests
18*	M	31	German	Carpenter	Healed tuberculosis
19	M	34	American	Clerk	Normal, but examination not completed
20*	M	42	Irish	Laborer	Roentgenographic proof of active tuberculosis
21*	M	56	German	Clerk	Cardiovascular renal condition
22	M	38	German	Machinist	Exophthalmic goiter
23*	M	54	Dutch	Machinist	Healed tuberculosis
24*	M	30	Irish	Waiter	Healed tuberculosis
25*	M	35	Austrian	Laborer	Roentgenographic evidence of active tuberculosis
26*	M	30	American	Electrician	Syphilis
27	M	30	Negro	Laborer	Syphilis; lead poisoning
28*	M	43	American	Electrician	Healed tuberculosis
29*	M	43	German	Cook	Urine contains bile pigment; subject presents a number of other abnormalities
30*	M	42	Irish	Porter	Cardiovascular renal condition
31	F	42	American	Housewife	Exophthalmic goiter
32*	M	26	American	Salesman	Cardiovascular renal condition
33	M	37	American	Laborer	Epileptic
34*	M	41	American	Railroad worker	Changes in capillaries of the skin; healed tuberculosis
35*	M	44	German	Clerk	Normal
36*	M	43	American	Clerk	Cardiovascular renal condition
37*	M	45	Irish	Miner	Normal
38	M	39	Jewish	Druggist	Angioneurotic edema
39*	M	35	Polish	Porter	Syphilis
40*	M	40	German	Houseman	Capillaries of the skin abnormal
41*	M	40	English	Machinist	Normal
42*	M	33	American	Fireman	Cardiovascular renal condition (myocarditis)
43*	M	45	American	Steamfitter	Normal
44*	M	48	American	Porter	Normal
45*	M	39	American	Painter	Cardiovascular renal condition
46*	M	29	American	Carpenter	Inanition; died later at Cook County Hospital (bronchopneumonia); fainted during examination
47*	M	38	American	Painter	Healed tuberculosis
48*	M	46	American	Woodworker	Syphilis
49*	M	42	Italian	Laborer	Cardiovascular renal condition
50*	M	20	German	Mason	Normal
51	F	58	German	Housewife	Exophthalmic goiter
52*	M	36	German	Steel worker	Healed tuberculosis
53*	M	39	Swedish	Laborer	Normal
54*	M	49	American	Fireman	Cardiovascular renal condition; probably cirrhosis; myocarditis
55*	M	51	American	Metal worker	Cardiovascular renal condition
56*	M	44	English	Fireman	Roentgenographic evidence of active tuberculosis 3 years before; angioneurotic edema
57	F	39	German	Housewife	Postoperative hypothyroidism; on thyroid extract, with basal metabolic rate +31.5

* One of group of 100 "normal" men.

TABLE 1.—*General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation—Continued*

Individual No.	Sex	Age	Nationality	Occupation	Clinical Notes
58	F	29	American	Housewife	Exophthalmic goiter
59*	M	37	Irish	Butcher	Normal
60	M	52	American	Salesman	Cardiovascular renal condition
61*	M	51	American	Musician	Cardiovascular renal condition
62*	M	44	American	Carpenter	Cardiovascular renal condition; aortic regurgitation
63*	M	40	American	Fireman	Cardiovascular renal condition
64*	M	31	American	Machinist	Normal, somewhat nervous
65*	M	34	American	Fireman	Cardiovascular renal condition
66*	M	64	American	Engineer	Cardiovascular renal condition
67*	M	47	American	Porter	Dwarf
68*	M	35	American	Draftsman	Healed tuberculosis
69	M	22	Jewish	Student	Duodenal ulcer; nervous; parents both have high blood pressure
70*	M	65	German	Butcher	Cardiovascular renal condition; arthritis deformans
71*	M	42	Scotch	Cook	Cardiovascular renal condition
72*	M	42	Scotch	Laborer	Normal
73*	M	48	American	Engineer	Syphilis
74*	M	49	American	Clerk	Changes in the capillaries of the skin
75*	M	66	American	Laborer	Cardiovascular renal condition
76*	M	43	American	Cook	Cardiovascular renal condition
77*	M	39	Irish	Machinist	Sensitized; drug addict?
78*	M	33	American	Painter	Normal, but with many deviations in examinations
79*	M	58	American	Machinist	Gastric ulcer; occasional peripheral vascular spasms
80*	M	29	American	Electrician	Nervous; has tremor; urticaria in 1922
81*	M	69	American	Elevator operator	Cardiovascular renal condition; pruritis
82*	M	66	English	Laborer	Cardiovascular renal condition
83*	M	45	German	Fireman	Normal
84*	M	73	Canadian	Foundry worker	Cardiovascular renal condition
85*	M	45	American	Tile setter	Fever (bronchitis?)
86*	M	50	American	Exdentist	Nervous
87*	M	46	American	Chauffeur	Normal
88*	M	55	American	Factory worker	Roentgenographic evidence of active tuberculosis
89*	M	41	Irish	Sailor	Healed tuberculosis
90*	M	30	American	Mail sorter	Nervous
91*	M	91	Irish	Gardener	Cardiovascular renal condition
92*	M	22	Jewish	Student	Nervous
93*	M	53	American	Laborer	Cardiovascular renal condition; hay-fever
94*	M	57	American	Laborer	Normal
95*	M	54	German	Cook	Healed tuberculosis
96*	M	70	American	Ironworker	Cardiovascular renal condition
97*	M	53	American	Miner	Normal; nervous
98*	M	34	American	Railroad worker	Cardiovascular renal condition
99*	M	46	Norwegian	Laborer	Healed tuberculosis
100*	M	45	Norwegian	Laborer	Healed tuberculosis
101*	M	55	American	Laborer	Eczema
102*	M	65	American	Metal worker	Roentgenographic evidence of active tuberculosis
103*	M	59	American	Rancher	Cardiovascular renal condition
104*	M	76	American	Laborer	Roentgenographic evidence of active tuberculosis; cardiovascular renal condition
105*	M	56	American	Painter	Healed tuberculosis
106*	M	60	American	Cook	Cardiovascular renal condition
107*	M	62	American	Sailor	Cardiovascular renal condition
108*	M	67	American	Clerk	Roentgenographic evidence of active tuberculosis
109	F	42	American	None	Neurasthenia
110*	M	62	American	Teamster	Healed tuberculosis
111*	M	60	American	Clerk	Cardiovascular renal condition; syphilis 30 years before
112*	M	60	American	Wool sorter	Cardiovascular renal condition
113*	M	59	Irish	Butcher	Cardiovascular renal condition
114*	M	79	English	Engineer	Roentgenographic evidence of active tuberculosis; cardiovascular renal condition
115*	M	66	American	Telegrapher	Cardiovascular renal condition
116	F	30	English	Clerk	Urticaria
117	M	30	English	Stockman	Arthritis; syphilis
118	F	14	American	Schoolgirl	Arthritis; pleural tuberculosis?

* One of group of 100 "normal" men.

TABLE 1.—*General Data from Histories of One Hundred and Seventy-Four Persons Employed in the Study of the Correlation of Constitutional Factors in Inflammation—Continued*

Individual No.	Sex	Age	Nationality	Occupation	Clinical Notes
119	F	43	Dutch	Housewife	Arthritis deformans; adenoma of thyroid with hyperthyroidism
120	F	18	Hungarian	Housework	Purpura
121	F	56	American	Housewife	Arthritis deformans
122*	M	33	American	Instructor	Normal; fatigue; numerous deviations from normal in examinations
123	F	68	American	Housewife	Carcinoma of thyroid; hyperthyroidism; cardiovascular renal condition
124	F	25	American	Nurse	Arthritis with mitral lesion
125	F	29	American	Housewife	Exophthalmic goiter
126	M	21	American	Metal polisher	Exophthalmic goiter
127*	M	65	Irish	Janitor	Cardiovascular renal condition
128*	M	66	American	Railroad worker	Hay-fever; cardiovascular renal condition
129*	M	66	Irish	Janitor	Roentgenographic evidence of active tuberculosis; cardiovascular renal condition
130*	M	65	Irish	Mason	Cardiovascular renal condition
131	F	59	Austrian	Housewife	Exophthalmic goiter
132	M	26	American	Student	Eczema
133	F	29	Jewish	Housewife	Generalized scleroderma
134*	M	67	American	Carpenter	Cardiovascular renal condition
135	M	26	Jewish	Tailor	Nervous
136	M	44	Italian	Laborer	Pellagra; cardiovascular renal condition
137	F	61	Bohemian	Housewife	Glaucoma
138	M	27	Jewish	Salesman	Fröhlich's syndrome
139	F	29	American	Stenographer	Vitiligo and urticaria
140	M	45	Irish	Laborer	Glaucoma; cardiovascular renal condition; roentgenographic evidence of active tuberculosis; hay-fever
141	F	48	Negro	Housewife	Glaucoma; cardiovascular renal condition
142	M	50	American	Machinist	Brain tumor, Cook County Hospital; syphilis 20 years before
143	M	45	Hungarian	Carpenter	Pellagra; cardiovascular renal condition; syphilis
144	M	47	Lithuanian	Carpenter	Pellagra; cardiovascular renal condition
145	M	71	Swedish	Watchman	Glaucoma; syphilis
146	F	40	American	Sewing	Myasthenia gravis
147	F	19	Polish	Operator	Postencephalitic parkinsonism
148	F	67	American	Housewife	Glaucoma; vitiligo; hay-fever
149	M	35	American	Salesman	Nervous
150	M	67	Jewish	Teamster	Glaucoma
151	F	68	German	Housewife	Postoperative exophthalmic goiter (no. 51)
152	M	27	American	Plumber	Angioneurotic edema
153	M	75	American	Farmer	Glaucoma; cardiovascular renal condition
154	M	55	American	Steel worker	Glaucoma; cardiovascular renal condition
155	M	33	American	Engineer	Postoperative exophthalmic goiter (no. 16)
156	F	30	American	Housewife	Postoperative exophthalmic goiter (no. 125)
157	M	38	American	Plumber	Postoperative exophthalmic goiter (no. 22)
158	M	35	Bohemian	Butcher	Hodgkin's disease
159	M	53	American	Clerk	Exophthalmic goiter
160	M	58	English	Shoemaker	Glaucoma; cardiovascular renal condition; asthma
161	F	43	American	Housewife	Glaucoma; cardiovascular renal condition
162	M	47	German	Railroad worker	Postoperative exophthalmic goiter (no. 11)
163	F	29	American	Housewife	Postoperative exophthalmic goiter (no. 58)
164	M	48	Cuban	Salesman	Glaucoma; syphilis; cardiovascular renal condition
165	M	52	American	Upholsterer	Glaucoma; cardiovascular renal condition
166	M	24	Hindoo	Student	Asthenia; eosinophilia
167	F	77	Swiss	Housewife	Glaucoma; cardiovascular renal condition
168	M	28	American	Physician	Orthostatic albuminuria
169	M	27	American	Chauffeur	Buerger's disease; syphilis
170	F	56	Negro	Servant	Glaucoma; diabetes; cardiovascular renal condition
171	F	23	Jewish	Technician	Urticaria (menstrual)
172	M	30	Greek	Waiter	Raynaud's disease; syphilis in 1921
173	M	39	American	Instructor	Cord tumor
174	F	50	American	Housework	Raynaud's disease

* One of group of 100 "normal" men.

Chart 1.—The scale of the blister time (heavy line) of normal persons and patients with various clinical conditions.

It will be observed that the blister time varies from a short time of 3½ hours in one case to 15 hours in a group of cases. The average for our group of 100 "normal" men is 7½ hours; this is indicated by the horizontal line.

Persons of the actually normal group (twenty in number) are designated by a star in the circle, in the first line below the curve. The range for these is from 4 to 9 hours. As the person (no. 122) with the four-hour blister time is abnormal in several other respects, we have not considered 4 hours as within the true normal range. The normal range is indicated by the shaded diamond in the center of the chart, in case of normal blister time having been placed between 6 and 9 hours.

Individuals of the group who showed healed tuberculosis are indicated by the large crosses in the next line. Individuals of the group with cardiovascular renal conditions of the group who gave roentgenologic evidence of healed tuberculosis are indicated by a small cross placed in the same horizontal space. The persons with positive Wassermann reactions and those with a clear history of previous syphilis are indicated by *W* in the same space. Patients who gave roentgenologic evidence of active tuberculosis can be identified by a black block in the third horizontal space. Those in the various groups of the division with cardiovascular renal conditions can be identified by the devices in the five lowest horizontal compartments, as follows:

A patient having a low blood pressure (under 110) with the urine containing either albumin or casts.

A patient having a normal blood pressure (from 110 to 140) with positive evidence of urinary changes.

A patient having a blood pressure of over 140 with positive evidence of urinary changes.

A patient having a blood pressure of over 140 with no evidence of changes in the urine.

A patient having roentgenologic evidence of arteriosclerosis of the larger vessels. When this has been found incidental to other clinical conditions, a small circle has been used.

A person in whom the capillaries of the skin are abnormal. A small *c* has been used to indicate that changes in the capillaries of the skin have been found incidental to other clinical conditions.

All the large symbols used in these lower five horizontal columns refer to the group of 100 "normal" men.

At the top of the curve we have used *G* to indicate the patients with glaucoma and × *G* to indicate those with exophthalmic goiter. In some charts, the individual numbers of the patients have been appended in the uppermost horizontal column.

An *N* along the curve indicates a nervous person, and an *S* a person who has been sensitized.

This explanation applies to all charts.

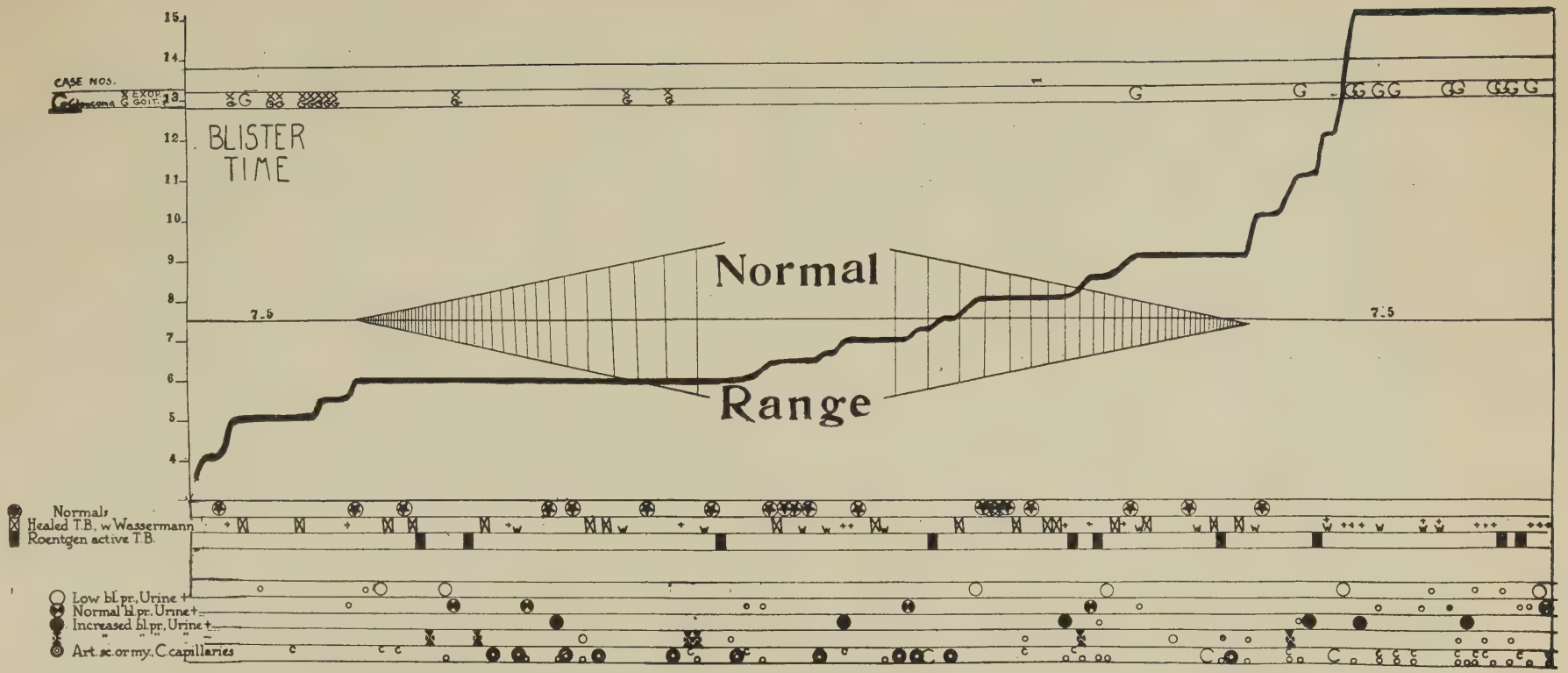
CASE NOS.
Glycosuria
EXOP. GOIT.
BLISTER TIME
Normal
Range
7.5
7.5
15
14
13
12
11
10
9
8
7
6
5
4
Normals
Healed T.B. w Wassermann
Roentgen active T.B.
Low bl. pr. Urine +
Normal bl. pr. Urine +
Increased bl. pr. Urine +
Art. sc. or my. C. capillaries

Chart 1

TABLE 2.—*The Results of Examinations of the Twelve Persons with the Shortest Blister Time*

Individual Number	Blister Time, Hours	Diagnosis	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Minutes	Age	Ice Reaction Time, Seconds	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Arteriosclerosis and Changes in Capillaries	Changes in Urine
116	3.5	Urticaria	10	19.4	1.94	30	30	20	Vagotonic	20.4	7.4	..	..
69	4	Ulcer and nervous	9.6	16	1.66	120	22	20	Sympatheticotonic	21.2	10	..	..
152	4	Angioneurotic edema	9.8	20.1	2.05	60	27	15	Vagotonic	26	7.5	..	+
122*	4	Normal	10.6	19.2	1.81	...	33	5	Vagotonic	20	7.8	..	..
7	4.25	Ulcer	....	....	....	...	25	..	.....	....	....	..	..
47*	5	Healed tuberculosis	10.4	26.2	2.51	90	38	15	Vagotonic	21.6	5.2	..	..
124	5	Heart disease; arthritis	10.5	....	....	90	25	10	Vagotonic	15.2	2.6	..	..
161	5	Glaucoma	9.17	18.03	1.96	75	43	12	Sympatheticotonic	14	13	..	Trace†
171	5	Urticaria	12.66	17.89	1.42	75	23	20	Sympatheticotonic	17	10.5	..	Trace†
38	5	Angioneurotic edema	9.8	21	2.14	90	39	10	Vagotonic	18	8.6	+	..
10*	5	Healed tuberculosis	10.1	24.6	2.4	150	40	7	Vagotonic	22.4	8.4	..	..
5	5.5	Neurosis	11.9	25.7	2.16	75	48	..	Vagotonic	....	....	..	Trace†
Averages	4.6		10.4	20.81	2.005	85.5	32.7	13.4		19.58	8.1		

* One of group of 100 "normal" men.
† Albumin.

TABLE 3.—*The Results of Examinations of the Twenty-Three Persons with a Prolonged Blister Time of Fifteen Hours*

Individual Number	Blister Time, Hours	Diagnosis	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Minutes	Age	Ice Reaction Time, Seconds	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Arteriosclerosis and Changes in Capillaries	Changes in Urine
167	15	Glaucoma	12	22.7	....	120	77	5	Sympatheticotonic	17	14	+	..
150	15	Glaucoma	12	21.3	1.78	95	67	7	Vagotonic	17	14	..	+
86*	15	Nervous	12.6	15.9	1.26	105	50	25	Vagotonic	18.8	14	..	..
145	15	Glaucoma	10.1	15.7	1.55	180	71	20	Sympatheticotonic	18	13.6	Arteriosclerosis and Wassermann ++++	+
146	15	Myasthenia gravis	9.2	14.4	1.56	105	40	30	Vagotonic	18	12	..	..
148	15	Glaucoma	9.7	24.3	2.5	85	67	10	Vagotonic	18	12	+	..
147	15	Parkinsonism	9.8	19.7	2	105	19	25	Sympatheticotonic	18	11.6	..	..
144	15	Pellagra	9.8	17.6	1.79	120	47	10	Sympatheticotonic	14.4	11.5	+	..
140	15	Pellagra	9.7	16.9	1.74	110	45	15	Sympatheticotonic	16.6	11.3	..	Albumin
158	15	Hodgkin's disease	9.33	18.53	2	60	49	35	Sympatheticotonic	19.2	11.3	..	Albumin
169	15	Buerger's disease	12.34	19.24	1.56	120	27	25	Vagotonic	20.8	11	Wassermann positive	..
107*	15	Glaucoma	8.1	18.2	2.24	130	61	30	Vagotonic	15.4	10.5	..	Albumin
154	15	Glaucoma	....	23.08	....	90	55	20	.....	23	10	+	..
104*	15	Cardiovascular renal condition	9.9	15.4	1.56	80	67	12	Sympatheticotonic	23.6	9.8	+	+
106*	15	Pellagra	10	18.8	1.88	105	44	45	Sympatheticotonic	20	9.5	+	+
79*	15	Ulcer	11.2	20	1.78	240	58	20	Sympatheticotonic	19.2	9.4	+	..
160	15	Glaucoma	10.86	21.58	1.98	70	58	10	Vagotonic	16	8	+	..
140	15	Glaucoma and tuberculosis	11.4	29.7	2.61	150	45	40	Vagotonic	18	8	..	..
170	15	Glaucoma	10.6	23.7	2.2	...	56	56	.....	....	....	+	..
129*	15	Tuberculosis	11.5	19	1.65	90	66	17	Vagotonic	18.4	7	..	Casts
155	15	Glaucoma	9	18.7	2.08	90	75	30	Sympatheticotonic	22	6.5	+	Casts
130	15	Cardiovascular renal condition	10.4	15.5	1.49	120	65	15	.....	20	5.4	+	+ Casts
128*	15	Cardiovascular renal condition	10.2	19.7	1.93	240	66	24	Sympatheticotonic	....	....	..	Albumin
Averages	15		10.4	19.5	1.86	118	55.4	21.3		18.6	10.4		

* One of group of 100 "normal" men.

the curve representing increased blister time; those with exophthalmic goiter are at the end representing shortened blister time.

In tables 2 and 3, we present the details of the examinations of the twelve persons with the shortest blister times and of the twenty-three with a blister time of approximately fifteen hours. In practically all other tabulations, we have selected the twenty showing the extreme reactions.[1]

From tables 2 and 3, the following conclusions seem warranted: Of the twenty-three persons with a prolonged blister time (table 2), twenty show roentgenologic evidence of arteriosclerosis, a positive Wassermann reaction or urinary changes (90 per cent). In the group with the shortest blister times there are none with arteriosclerosis, only one with capillary change and four (25 per cent) with trace of albumin in the urine.

The group in which blister formation is prolonged has a slightly lower level of potassium and a lower K/Ca ratio. The Kromayer light erythema time is longer, as is the reaction to ice. The persons are much older. There are fewer vagotonic reactions to epinephrine and, though the wheal due to the intracutaneous injection of epinephrine hydrochloride is small, the flare is large.

It will be noted that the types of diseases of the one group are different from those of the other group.

CAPILLARY PERMEABILITY

Permeability of the capillaries of the skin, as estimated by the relative proportion of protein in a cantharides blister as compared with the protein in the serum of the capillary blood, averages 62 for the group of 100 "normal" men. In a previous study [2] of sixty-six normal students in an age group of from 22 to 25, we found the average permeability to be 68, and in another study [3] of a small group of young women during the intermenstrual period, we found it to be 72.

The average for our strictly normal group is also 62. When we examine chart 2, we find that a number of the normal persons are grouped at the low end of the scale. In three of the four lowest,

1. Patients with exophthalmic goiter have not been included because we have felt that the extreme changes associated with the disease might tend to distort the averages.

2. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Skin Blister, Arch. Int. Med. **38**:663 (Nov.) 1926.

3. Petersen, W. F., and Milles, G.: The Relation of Menstruation to the Permeability of the Skin Capillaries and the Autonomic Tonus of the Skin Vessels, Arch. Int. Med. **38**:730 (Dec.) 1926.

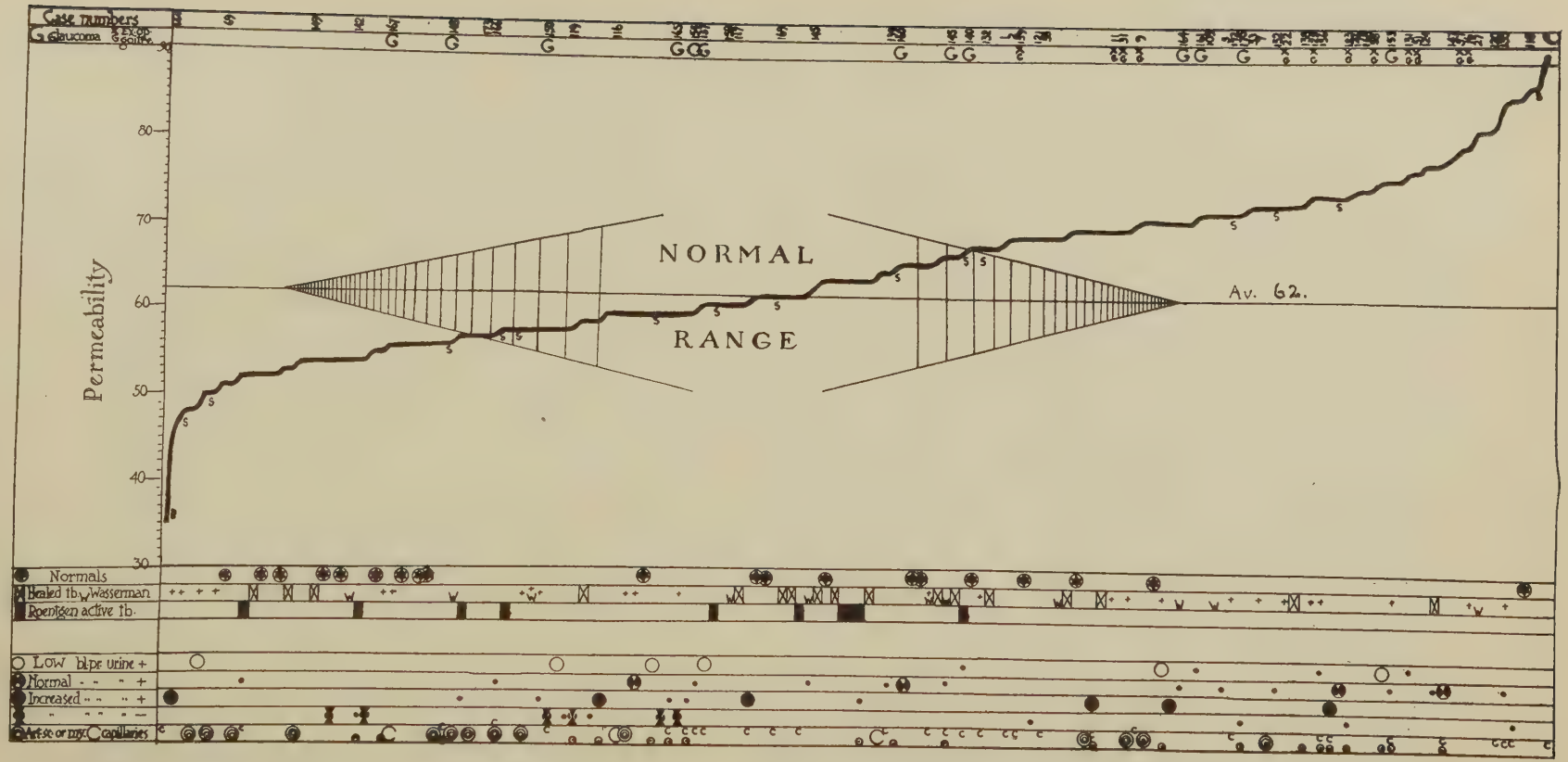

Chart 2.—The permeability of the capillaries of the skin (indicated by heavy line) of normal persons and patients with various clinical conditions. An explanation of the grouping of the normal persons and patients along the curve is given in the legend for chart 1.

TABLE 4.—*The Results of Examinations of the Twenty Persons Having the Lowest Permeability of the Capillaries*

Individual Number	Permeability of Capillaries	Diagnosis	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Weight/Length Ratio	Age	Changes in Capillaries	Changes in Urine
144	35	Pellagra	14.4	11.5	15	0	174	47	+++	0
115	46	Cardiovascular renal condition	17.2	6.2	14.2	8	215	66	..	Trace albumin
101	47	Sensitized	19.6	7	10	0	191	55	Dilatation	..
42	47	Cardiovascular renal condition	19.2	11.8	9.2	4.6	241	33	..	..
127	50	Cardiovascular renal condition	18.4	9.7	15.4	12	180	65	..	Albumin, casts
93	50	Cardiovascular renal condition; sensitized	20.4	8.6	10	0	267	52	0	..
69	51	Nervous and ulcer	21.2	10	14.4	10.2	160	22	..	..
83	51	Normal	17.2	9.2	13.4	11	258	45	Delayed	..
103	52	Cardiovascular renal condition	22.4	9	12.2	0	270	59	..	..
129	52	Tuberculosis; cardiovascular renal condition	18.4	7	12.7	0	249	66	Granulation, sluggish	Casts
89	52	Healed tuberculosis	20.8	9.8	10.2	0	204	41	..	..
59	52	Normal	22	7.2	15.6	8	252	37	..	..
62	52	Aortic regurgitation	17.2	7	11.4	7.8	221	44	..	..
94	53	Normal	20	6	11.2	7.8	236	57	Slow	..
100	53	Healed tuberculosis	18.8	8.6	12	29.2	241	45	..	..
112	54	Cardiovascular renal condition	22.4	7.2	9.8	0	218	60	..	..
149	54	Nervous	20	9.7	19	0	209	35	..	..
110	54	Edema; healed tuberculosis	20.8	4.2	12	9.4	190	62	Diminished	..
35	54	Normal	22.8	11	9.2	0	203	44	..	..
45	54	Cardiovascular renal condition	20.4	9.8	16.4	12	317	39	..	..
	50	Averages and totals	19.6	8.5	12.7	6	224	48.7	2 (granulation)	3

TABLE 5.—*The Results of Examinations of the Twenty Persons Having the Highest Permeability of the Capillaries*

Individual Number	Permeability of Capillaries	Diagnosis	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Weight/Length Ratio	Age	Changes in Capillaries	Changes in Urine
80	91	Nervous	14.8	12.4	13.4	9.2	212	29	Granulation	..
77	87	Sensitized	14	10.8	10	15.4	187	39	..	..
118	87	Arthritis, tuberculosis	16.8	7.4	12	8.6	154	14	..	..
78	86	Normal	19.6	12	12.4	6.2	203	33	..	..
79	86	Ulcer	19.2	9.4	8.2	12.2	220	58	Tortuosity	..
135	84	Nervous	12.4	3.2	20	0	183	26	Granulation	Casts
120	82	Purpura	21.2	7.2	12.1	0	172	18	Granulation	..
92	82	Nervous	20.4	10.2	15.2	7.6	210	22	..	..
27	82	Lead poisoning and syphilis	....	....	....	....	217	30	..	..
147	79	Parkinsonism	18	11.6	13	0	142	19	..	..
66	78	Cardiovascular renal condition	20	9.2	10.2	6	257	64	Granulation	+
68	78	Healed tuberculosis	19.2	9.6	12	7	217	35	Rapid flow	Trace albumin
124	78	Arthritis; heart disease	15.2	2.6	....	....	210	25	Diminished flow	..
153	76	Glaucoma, decompensation	22	6.5	18	0	223	75	Dilatation	+ Casts
76	76	Cardiovascular renal condition	20	6.6	11	7	230	43	..	Granular casts
168	75	Orthostatic	18	16	14	0	215	28	..	Albumin
146	75	Myasthenia	18	12	19	0	192	40	..	..
14	74	Cardiovascular renal condition	24.4	6.2	15	5	198	36	..	Casts
70	74	Cardiovascular renal condition	18	11	10	0	264	65	Slow	Casts, albumin
136	74	Pellagra	20	9.5	18	0	180	44	Granulation	Albumin
	80	Averages and totals	18.3	9.1	13.4	4.3	204	37	7 (granulation)	9

the examination of the capillaries of the skin revealed that the capillary flow was sluggish or that the number of capillaries was diminished. While, therefore, we cannot regard these persons as abnormal, the change in the flow of the capillaries of the skin must be considered in connection with their diminished permeability. On the other hand, we note that the end of the scale representing higher permeability reveals more persons in whom distinct anatomic changes could be observed in the capillaries in the form of granulations, marked dilatations, etc.

Healed tuberculosis (revealed by roentgen examination) is found at all levels, but the cases in which there is roentgenologic evidence of active tuberculosis are found at the normal or lower levels of permeability. It should be emphasized that these cases are not necessarily clinically active; in the clinically active cases, the tendency is toward greater permeability with progression of the disease.[4] (In chart 2, persons with roentgenologic evidence of healed tuberculosis other than those of the group of 100 "normal" men are indicated by the cross in the horizontal column designated "Healed Tuberculosis.")

It will be noted that the arteriosclerotic or myocarditic (revealed by roentgen examination) cases are equally common in both regions of the scale. But of the eighteen persons with arteriosclerosis on the side of lower permeability, only five have urinary changes, while of the seventeen on the side of higher permeability, ten have urinary changes.

There are, furthermore, nine with increased blood pressure (over 140), but without urinary changes, in the group of less permeability as compared with four in the group of more permeability.

Capillary changes, i. e., granulations, occur in eleven in the group below the average and in twenty in the group above.

Sensitized persons are reported in all the ranges.

The increased permeability coincident with exophthalmic goiter is apparent.

In table 4, we have tabulated the results of some examinations of the twenty persons with the lowest permeability and in table 5, of those with the highest permeability (excluding those with exophthalmic goiter).

When we examine the averages of tables 4 and 5, we find, of course, that the persons with lessened permeability are older and heavier.

INFLAMMATORY INDEX

The group with low inflammatory indexes is partly identical with a series showing prolonged blister time, i. e., persons of advanced age, with cardiovascular renal lesions or with other evidences of chronic disease.

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4. Levinson, S. A., and Petersen, W. F.: Am. Rev. Tuberc. **15**:681, 1927.

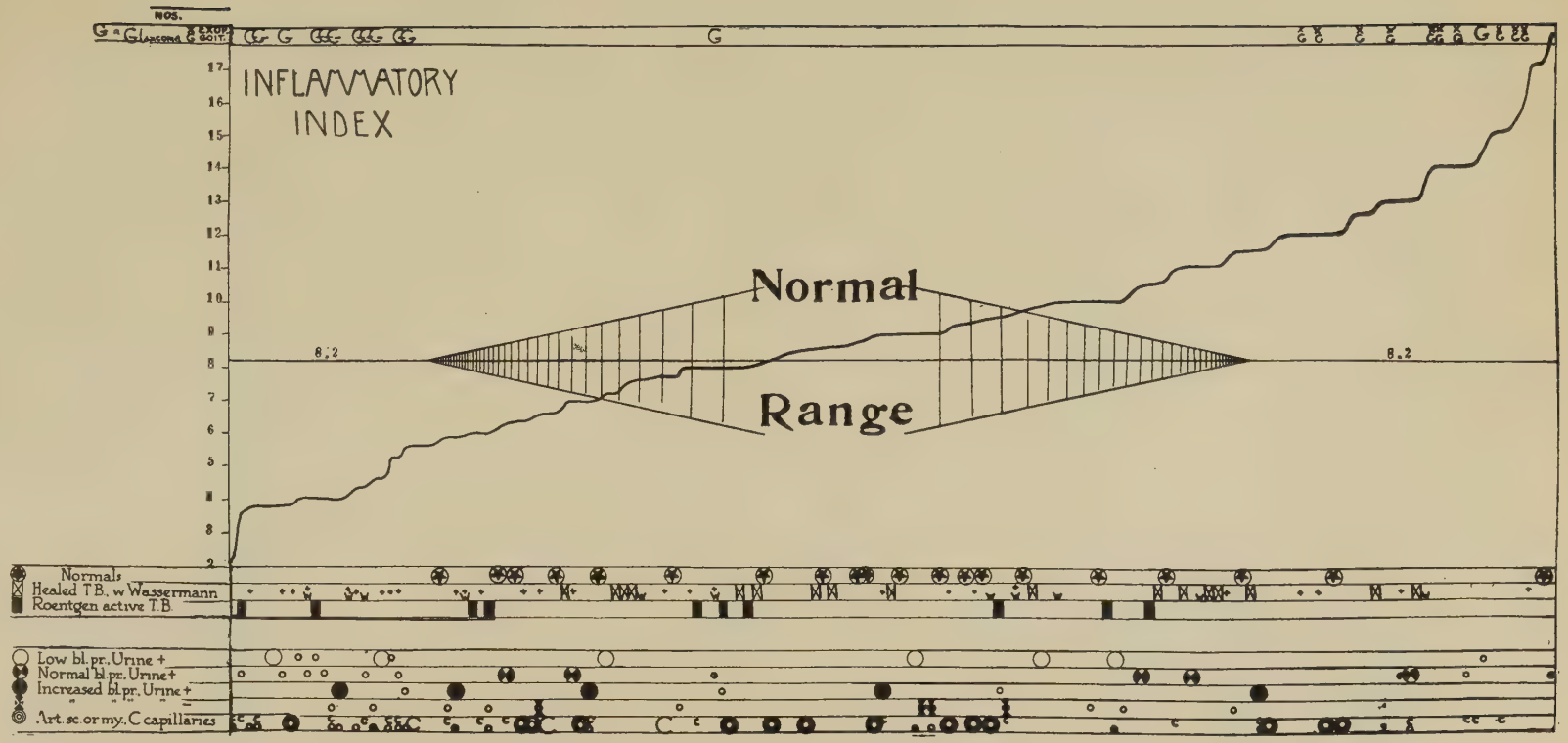

Chart 3.—The inflammatory index (heavy line) of normal persons and patients with various clinical conditions.

TABLE 6.—*The Results of the Examinations of the Twenty Persons Having the Lowest Inflammatory Indexes*

Individual Number	Inflammatory Index	Diagnosis	Blister Time, Hours	Permeability of Capillaries	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Mn.	Carbon Dioxide Combining Power	Ice Reaction Time, Seconds	Age	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)
136	5	Pellagra	15	74	10	18.8	1.88	105	57.9	45	44	Sympatheticotonic	20	9.5	18	0
130*	4.7	Cardiovascular renal condition	15	71	10.4	15.5	1.49	120	55.6	15	65	.....	20	5.4	11.2	0
170	4.6	Aortic syphilis; bronchiectasis; glaucoma	15	72	10.5	23.7	2.2	...	52.5	..	56	.....	....	....	....	....
145	4.4	Glaucoma	15	67	10.1	15.7	1.55	180	55.4	20	71	Sympatheticotonic	18	13.6	16	0
160	4.4	Asthma; emphysema; bronchiectasis; glaucoma	15	66	10.8	21.5	1.98	70	62.7	10	58	Vagotonic	16	8	20	0
169	4.1	Buerger's disease	15	62	12.3	19.2	1.56	120	55.1	25	27	Vagotonic	20.8	11	18	0
134*	4	Cardiovascular renal condition	15	60	9.9	15.4	1.56	80	54.8	12	67	Sympatheticotonic	23.6	9.8	19.2	9.6
154	4	Glaucoma	15	60	....	23	....	90	56.6	20	66.6	Vagotonic	23	10	26	0
137	4	Cardiovascular renal condition; glaucoma	15	61	8.1	18.2	2.24	130	51.9	30	61	Sympatheticotonic	15.4	10.5	13	0
140	4.05	Cardiovascular renal condition; glaucoma	15	68	11.4	29.7	2.61	150	55.6	40	45	Vagotonic	18	8	27	0
143	4	Pellagra	15	63	9.7	16.9	1.74	100	55.4	15	45	Sympatheticotonic	16.6	11.3	9	0
158	4	Hodgkin's disease; cardiovascular renal condition	15	61	9.3	18.5	2	60	57.8	35	49	Sympatheticotonic	19.2	11.3	28	0
123*	3.8	Cardiovascular renal condition	15	58	10.2	19.7	1.93	240	58.1	24	66	Sympatheticotonic	....	....	14.4	0
150	3.8	Glaucoma	15	58	12	21.3	1.78	95	72.7	7	67	Sympatheticotonic	17	14	16	0
127*	3.8	Cardiovascular renal condition	13	50	12.2	16.2	1.67	255	59.1	16	65	Sympatheticotonic	18.4	9.7	15.4	12
86*	3.8	Nervous	15	58	12.6	15.9	1.26	105	55	25	50	Vagotonic	18.8	14	15.4	12.4
148	3.7	Glaucoma	15	56	9.7	24.3	2.5	85	69.5	10	67	Sympatheticotonic	18	12	17	0
167	3.7	Bronchiectasis; glaucoma	15	56	12	22.7	1.9	120	47.9	5	77	.....	17	14.2	15	0
129*	3.5	Tuberculosis; cardiovascular renal condition	15	52	11.5	19	1.65	90	61.6	17	66	Vagotonic	18.4	7	12.2	0
144	2.2	Cardiovascular renal condition; pellagra	15	35	9.8	17.6	1.76	120	54.4	10	47	Sympatheticotonic	14.4	11.5	15	0
	3.97	Averages and totals	14.9	60	10.6	19.64	1.85	121.8	57.48	20	57.4	5 V., 11 S.	18.47	10.6	17.14	11.3

* One of group of "normal" men.

TABLE 7.—*The Results of Examinations of the Twenty Persons Having the Highest Inflammatory Indexes*

Individual Number	Inflammatory Index	Diagnosis	Blister Time, Hours	Permeability of Capillaries	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Mn.	Carbon Dioxide Combining Power	Ice Reaction Time, Seconds	Age	Epinephrine, Vascular Reaction	Epinephrine, Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)
142	18	Angioneurotic edema	4	73	9.8	20.5	2.05	60	63.4	15	27	Vagotonic	26	7.5	9	8
122*	17	Normal	4	68	10.6	19.2	1.81	...	56.8	5	33	Sympatheticotonic	20	7.8	12	9
116	17	Urticaria	3.5	60	10	19.4	1.94	30	55.1	20	30	Vagotonic	20.4	7.4	5	0
80*	15.1	Cardiovascular renal condition; nervous	6	91	8.1	13.7	1.7	100	53.2	30	29	Sympatheticotonic	14.8	12.4	13.4	9.2
124	15	Heart disease	5	78	....	....	....	90	53.7	10	25	Vagotonic	15.2	2.6	....	....
161	14.5	Cardiovascular renal condition; glaucoma	5	72	9.17	18.03	1.96	75	49.4	12	43	Sympatheticotonic	14	13	13	0
38	14	Cardiovascular renal condition; angioneurotic edema	5	69	9.8	21	2.14	90	58.5	10	39	Vagotonic	18	8.6	10.2	10.4
135	14	Neurovascular syndrome	6	84	11.9	19.6	1.65	75	54.5	18	26	Vagotonic	12.4	3.2	20	0
171	14	Urticaria	5	73	12.66	17.89	1.42	75	48.7	20	18	.....	17.5	10.5	18	0
27	13.6	Lead poisoning	6	82	10	21.4	2.14	...	54.9	..	30	.....	....	....	....	....
10*	13	Neurovascular syndrome; healed tuberculosis	5	64	10.1	24.6	2.4	150	60.4	7	40	Sympatheticotonic	22.4	8.4	9	7.2
66*	13	Cardiovascular renal condition	6	78	11	20	1.82	15	53.1	28	54	Sympatheticotonic	20	9.2	10.2	0
5	13	Nervous	5.5	72	11.9	25.7	2.16	75	63.9	..	48	.....	....	....	....	....
120	13	Purpura	6	82	10	19.9	1.99	75	52.2	14	18	.....	21.2	7.2	12.1	0
47*	12.8	Healed tuberculosis	5	62	10.4	26.2	2.51	90	56.4	15	38	Vagotonic	21.6	5.2	9	0
69	12.7	Ulcer; nervous	4	51	9.6	16	1.66	120	54.8	20	22	Sympatheticotonic	21.2	10	14.4	10.2
79*	12.6	.....	6	76	....	....	....	120	57.6	..	..	.....	....	....	....	....
98*	12.1	Cardiovascular renal condition	6	73	8.8	17	1.93	105	62.7	15	34	Sympatheticotonic	20	4	11.2	0
78*	12	Normal	7	86	8.4	18.8	2.23	195	62.7	10	33	Sympatheticotonic	19.6	12	12.4	6.2
106*	12	Cardiovascular renal condition	6	71	11.2	19	1.69	90	49.5	30	60	Vagotonic	19.6	7	11.2	0
	13.92	Averages and totals	5.3	73.2	10.17	19.9	1.95	90.5	56.07	16.4	34	8 V., 8 S.	19	8	11.8	8.6

* One of group of 100 "normal" men.

If we examine chart 3, we observe the piling up of persons with arteriosclerosis, capillary changes and evidence of renal disease (albumin or casts) at the low end of the scale. It may also be observed that the majority of the patients with roentgenologic evidence of active tuberculosis are found in the low range, where, too, there are more persons with roentgenologic evidence of healed lesions. The patients with glaucoma and the associated prolonged blister time are also in this region.

The persons with high inflammatory indexes include those with diseases of the skin (urticaria and angioneurotic edema) and, of course, patients with exophthalmic goiter. It may be significant that none of those with increased blood pressure (over 140, with or without renal lesions) are found above the normal maximal range of 11.5.

When we examine tables 6 and 7, with the results of examinations in twenty of the extreme cases, several differences become apparent. The relation to permeability of the capillaries and blister time is, of course, obvious. The group of persons with the low inflammatory indexes are much older, their calcium levels are higher, their K/Ca ratios are lower, their Kromayer light erythema times and their ice reaction times are longer and their flares due to epinephrine and wheals due to thyroxin are larger.

There are proportionately more sympatheticotonic persons among those with low than among those with high indexes, despite the fact that persons with cardiovascular renal lesions are found more frequently at the low end of the scale.

CALCIUM, POTASSIUM AND K/CA RATIO

The relation of the calcium and the potassium and the K/Ca ratio of the blood serum of normal persons, as well as of patients ill from various diseases, has been studied with considerable interest in recent years. The relations to the autonomic reactions, in particular, have received much attention. Kylin,[5] as well as the Kraus school, showed definite relations to asthma [6] and hyperpiesis.[7]

In the previously published results of examinations of "normal" persons, no evidence was presented as to their actual physical normalcy. In our group of 100 "normal" men, only twenty could actually be as classified. The remaining eighty showed evidence of cardiovascular renal abnormality, healed or active tuberculosis, syphilis, etc.

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5. Kylin, E.: Acta med. Scandinav. (suppl.) **1**:112, 1927.
6. Kylin, E.: Klin. Wchnschr. **6**:1742, 1927.
7. Kylin, E.: Zentralbl. f. inn. Med. **48**:431, 1927.

Our determinations were made on fresh serum with the Clark-Collip method for calcium and the Kerr modification for potassium. The results have been tabulated in table 8.

Chart 4 may aid in making the conditions more apparent. It will be noticed that the K/Ca curve commences with a low ratio of 1.12 in a young man (no. 132) 25 years of age (whose interesting series of clinical manifestations of disease is described on page 74) and reaches a high ratio of 3.22 in a man 52 years of age (no. 93), who has had hay-fever each fall, is sensitive to halibut, shows x-ray evidence of myocarditis and is short of breath on exertion.

When we analyze the K/Ca ratios of the so-called normal group of 100, several interesting relations are to be observed.

Normal Persons.—In the first place, the actually normal persons fall, with two exceptions, within the range from 1.7 to 2.4. One of the two exceptions, with a ratio of 1.53, gives a markedly vagotonic reaction to epinephrine. The other, with a ratio of 2.9, is apparently healthy in every respect.

Persons with Roentgenologic Evidence of Healed Parenchymal Tuberculosis and Syphilis.—Of the seventeen persons with roentgenologic evidence of healed parenchymal tuberculosis, who are otherwise normal, eleven fall within the normal range, while seven of the nine syphilitic persons are also included within these limits. Tuberculosis, unless active, and syphilitic infection apparently do not materially alter the status.

Persons with Active Tuberculosis.—When one now turns to the group with roentgenologic evidence of active tuberculosis, one meets an interesting change. The average ratio for the entire group is 2.08, i. e., normal, but inspection of the chart will reveal that the ratios in the active cases are all outside the normal limits. Five persons have low ratios. Of these, one has albuminuria. These five all have low or normal blood pressure. The other five are at the extreme opposite end, with high K/ca ratios. Three of these have increased blood pressure, one normal blood pressure with albuminuria and the fifth a history of angioneurotic edema.

Persons with Cardiovascular Renal Lesions.—The persons with cardiovascular renal lesions are found scattered over the entire range of the K/Ca ratio without any apparent relation to blood pressure, to the degree of sclerosis of the larger vessels (made apparent on roentgen examination) or to capillary changes. There are no true cases of primary hypertension in the group, there being only some with an increase in blood pressure of from 140 to 170 (without changes in the kidneys),

TABLE 8.—*The K/Ca Ratios, the Potassium Values and the Calcium Values of One Hundred So-Called Normal Persons, as Well as of Patients with Glaucoma, Exophthalmic Goiter, Etc.*

Individual Number		K/Ca Ratio	Calcium, Mg.	Potassium, Mg.
132	Eczema sensitized	1.12	13.4	15
46*	Inanition; worry	1.24	13.8	17.4
86*	Inanition; previous angioneurotic edema	1.23	12.6	15.9
62*	Aortic regurgitation	1.3	12.2	15.2
133	Scleroderma	1.32	13.2	17.5
90*	Nervous	1.34	11.4	14.[illegible]
110*	Edema under eyes; roentgenographic evidence of healed tuberculosis	1.34	12.1	16.3
118	Arthritis; possibly tuberculosis of lungs	1.4	12.2	17.2
88*	Roentgenographic evidence of active tuberculosis	1.4	9.4	13
112*	Roentgenographic evidence of arteriosclerosis	1.4	12.6	18
171	Menstrual urticaria	1.4	12.66	17.9
173	Cord tumor; worry	1.43	12.7	18.7
17*†	Normal (vagotonic reaction to epinephrine)	1.43	12.7	18.2
77*	Previous sensitization	1.44	10.8	15.6
70*	Arthritis deformans; arteriosclerosis; nephritis	1.45	11.4	16.6
18*	Healed tuberculosis	1.46	14.5	21.2
108*	Roentgenographic evidence of active tuberculosis, chronic	1.47	10.4	15.3
3*	Healed tuberculosis; nervous	1.47	11.1	16.7
45*	Increased blood pressure ‡ (had nephritis as a result of scarlet fever)	1.48	11.2	16.6
130*	Nephritis; arteriosclerosis	1.49	10.4	15.5
109	Nervous; worry	1.5	10.8	16.1
82*	Increased blood pressure; changes in capillaries	1.5	11.4	17.2
22	Exophthalmic goiter	1.5	12.1	18.2
20*	Roentgenographic evidence of active tuberculosis	1.53	11.4	17.4
134*	Increased blood pressure; nephritis	1.56	9.9	15.6
60	Increased blood pressure; changes in capillaries	1.56	11.4	17.5
15*	Healed tuberculosis	1.55	12.1	18.8
111*	Arteriosclerosis; old syphilis	1.55	11.8	18.3
145	Changes in capillaries; glaucoma; arthritis; syphilis	1.55	10.1	15.7
42*	Myocarditis	1.56	11.4	17.8
146	Myasthenia gravis; idiosyncrasy	1.56	9.2	14.4
169	Sensitized; healed tuberculosis; Buerger's disease; syphilis	1.56	12.34	19.24
102*	Roentgenographic evidence of active tuberculosis	1.63	10.6	17.3
172	Sensitized; Raynaud's disease; healed tuberculosis	1.64	13	21.3
129*	Roentgenographic evidence of active tuberculosis; nephritis	1.65	11.5	19
135	Nervous; healed tuberculosis; nephritis	1.65	11.9	19.6
69	Nervous; increased blood pressure; ulcer; healed tuberculosis	1.66	9.6	16
65*	Nephritis; changes in capillaries	1.67	9.8	16.4
106*	Dilatation of aorta	1.69	11.2	19
127*	Nephritis; healed tuberculosis	1.68	9.7	16.2
131	Exophthalmic goiter	1.7	10.6	18
80*	Nervous; changes in capillaries; healed tuberculosis; previously sensitized	1.7	8	13.7
40*	Changes in capillaries	1.73	10.8	18.7
72*†	Normal	1.73	10.8	18.7
73*	Positive Wassermann reaction	1.74	11.2	19.5
143	Pellagra; syphilis	1.74	9.7	16.9
149	Nervous; worry	1.74	10.1	17.4
14*	Nephritis; sensitized	1.75	11.2	19.6
44*†	Normal	1.76	10	17.6
75*	Increased blood pressure	1.78	10.8	19.2
79*	Increased blood pressure; ulcer; changes in capillaries	1.78	11.2	20
84*	Albuminuria; changes in capillaries	1.78	10	17.8
150	Glaucoma; healed tuberculosis; hyaline casts	1.78	12	21.3
165	Glaucoma; dilated aorta; nephritis	1.79	10	17.95
144	Pellagra; changes in capillaries	1.79	9.8	17.6
117	Syphilitic arthritis	1.8	9.2	17.5
85*	Slight fever, unknown origin	1.8	10.6	19.1
74*	Changes in capillaries	1.8	11	19.9
6	Nephritis; arteriosclerosis; myocarditis	1.8	10.5	18.9
4*†	Normal	1.8	11.8	21.2
89*	Healed tuberculosis	1.81	9.2	16.7
105*	Healed tuberculosis	1.81	9	17.1
122*†	Normal	1.81	10.6	19.2
66*	Arteriosclerosis; myocarditis; hyaline casts	1.82	11	20
113*	Arteriosclerosis; healed tuberculosis	1.82	10.2	18.6
63*	Arteriosclerosis; healed tuberculosis	1.83	11.4	20.9
126	Exophthalmic goiter	1.83	9.8	18.3
64*†	Normal; slightly nervous	1.84	9	16.6
99*	Healed tuberculosis	1.86	9.6	17.9
76*	Nephritis; dilated aorta; granular casts	1.87	10.8	20.2
103*	Arteriosclerosis; myocarditis	1.88	9.2	17.3
136	Pellagra; arteriosclerosis; changes in capillaries	1.88	10	18.8
138	Fröhlich syndrome (?); myocarditis (?)	1.88	10.6	19.9

* Indicates that the person is one of the group of 100 so-called normal persons.
† Indicates that the person is apparently normal on examination.
¶ Changes in capillaries means increased dilatation or actual granulation and tortuosity
‡ Blood pressures of 140 or over are noted as increased.

TABLE 8.—*The K/Ca Ratios, the Potassium Values and the Calcium Values of One Hundred So-Called Normal Persons, as Well as of Patients with Glaucoma, Exophthalmic Goiter, Etc.—Continued*

Individual Number		K/Ca Ratio	Calcium, Mg.	Potassium, Mg.
168	Orthostatic albuminuria	1.88	9.4	17.7
43*†	Normal	1.89	9.2	19.4
164	Nephritis; glaucoma; syphilitic aortitis	1.89	8.7	16.54
139	Urticaria; vitiligo; changes in capillaries	1.9	9.7	18.4
167	Glaucoma; arteriosclerosis; changes in capillaries	1.9	12	22.72
16	Exophthalmic goiter; healed tuberculosis; changes in urine	1.9	11.4	21.6
39*	Syphilis	1.91	9.4	18
98*	Arteriosclerosis	1.93	8.8	17
128*	Arteriosclerosis; healed tuberculosis; albumin; changes in capillaries	1.93	10.2	19.7
68*	Healed tuberculosis	1.94	8.8	17.1
116	Urticaria	1.94	10	19.4
59*†	Normal	1.95	9.6	18.8
115*	Arteriosclerosis; albumin	1.95	7.8	15.2
142	Neoplasm (syphilis); arteriosclerosis	1.95	9.4	18.3
180	Neoplasm (mole)	1.96	11.11	21.86
161	Glaucoma; albumin; changes in capillaries	1.96	9.7	18.03
160	Glaucoma; healed tuberculosis; asthma	1.98	10.86	21.6
120	Purpura; changes in capillaries	1.99	10	19.9
174	Raynaud's disease ?	2	10.8	21.5
158	Hodgkin's disease	2	9.33	18.53
147	Epidemic encephalitis	2	9.8	19.7
71*	Arteriosclerosis	2	8.8	17.5
67*	Dwarf	2	8.8	17.6
52*	Healed tuberculosis	2	10.4	20.9
8*†	Normal	2	10.5	21
1	Nervous	2	12.1	24.9
2	Epilepsy; angioneurosis	2	12.9	26.1
9	Exophthalmic goiter; changes in capillaries	2.04	11.5	23.5
152	Angioneurotic edema; hyaline casts	2.05	9.8	20.1
101*	Healed tuberculosis; eczema	2.06	9.4	19.4
96*	Arteriosclerosis	2.07	8.2	17
94*†	Normal	2.08	8.4	17.5
153	Glaucoma; nephritis; healed tuberculosis	2.08	9	18.7
119	Adenoma of thyroid	2.1	9	18.7
24*	Healed tuberculosis	2.12	11.7	24.8
27	Syphilis; lead poisoning	2.14	10	21.4
38	Angioneurotic edema; changes in capillaries	2.14	9.8	21
58	Exophthalmic goiter	2.15	12	25.9
5	Healed tuberculosis	2.16	11.9	25.7
41*†	Normal	2.16	9.8	21.2
36*	Albuminuria	2.17	12.1	26.3
123	Carcinoma of thyroid; arteriosclerosis	2.17	9.2	20
159	Exophthalmic goiter	2.17	8.23	17.9
23*	Healed tuberculosis	2.19	13.1	28.6
28*	Healed tuberculosis	2.17	11	24.1
170	Diabetes, etc.; glaucoma; increased blood pressure	2.2	10.6	23.71
11	Exophthalmic goiter; healed tuberculosis	2.21	10.9	24.1
78*†	Normal	2.23	8.4	18.8
137	Glaucoma; albuminuria	2.24	8.1	18.2
37*†	Normal	2.26	10	22.6
121	Increased blood pressure; arthritis deformans	2.27	8.9	20.2
166	Eosinophilia of unknown origin	2.27	9.1	20.66
49*	Hyaline casts	2.29	11	25.2
107*	Arteriosclerosis; myocarditis	2.3	8	18.4
83*†	Normal	2.3	8.2	19
87*†	Normal	2.32	8.4	19.5
92*	Neurosis	2.32	8.4	19.5
30*	Arteriosclerosis; increased blood pressure	2.33	10.3	24
61*	Arteriosclerosis; changes in capillaries; albuminuria	2.35	7.6	17.6
97*†	Normal (nervous)	2.37	8.4	20.9
100*	Healed tuberculosis	2.38	9	21.5
29*†	Normal	2.39	10	23.9
114*	Tuberculosis; arteriosclerosis; nephritis	2.4	8	19.2
50*†	Normal	2.4	11.4	27.4
10*	Healed tuberculosis	2.4	10.1	24.6
95*	Healed tuberculosis	2.41	7.8	18.8
13*	Healed tuberculosis	2.48	9.6	23.8
148	Glaucoma; vitiligo; arteriosclerosis	2.5	9.7	24.3
47*	Healed tuberculosis	2.51	10.4	26.2
21*	Albuminuria; changes in capillaries	2.51	10.2	25.6
56*	Tuberculosis; has had angioneurotic edema	2.52	9.8	24.6
51	Exophthalmic goiter	2.58	10	25.8
25*	Tuberculosis; albuminuria	2.6	11.1	28.8
140	Glaucoma; tuberculosis; sensitized	2.61	11.4	29.7
26*	Syphilis	2.61	10.2	26.6
33	Epileptic	2.73	9.5	26.1
32*	Increased blood pressure	2.73	9.5	26.1
48*	Syphilis	2.87	9.6	27.6
34*	Changes in capillaries	2.89	9.6	27.7
35*†	Normal	2.9	8.7	25.2
81*	Arteriosclerosis; myocarditis; pruritis	3.07	8.4	25.8
104*	High blood pressure; tuberculosis; arteriosclerosis	3.09	7.4	22.9
55*	Albumin and hyaline casts; healed tuberculosis	3.1	8	24.9
93*	Sensitized; myocarditis	3.2	7.6	24.5

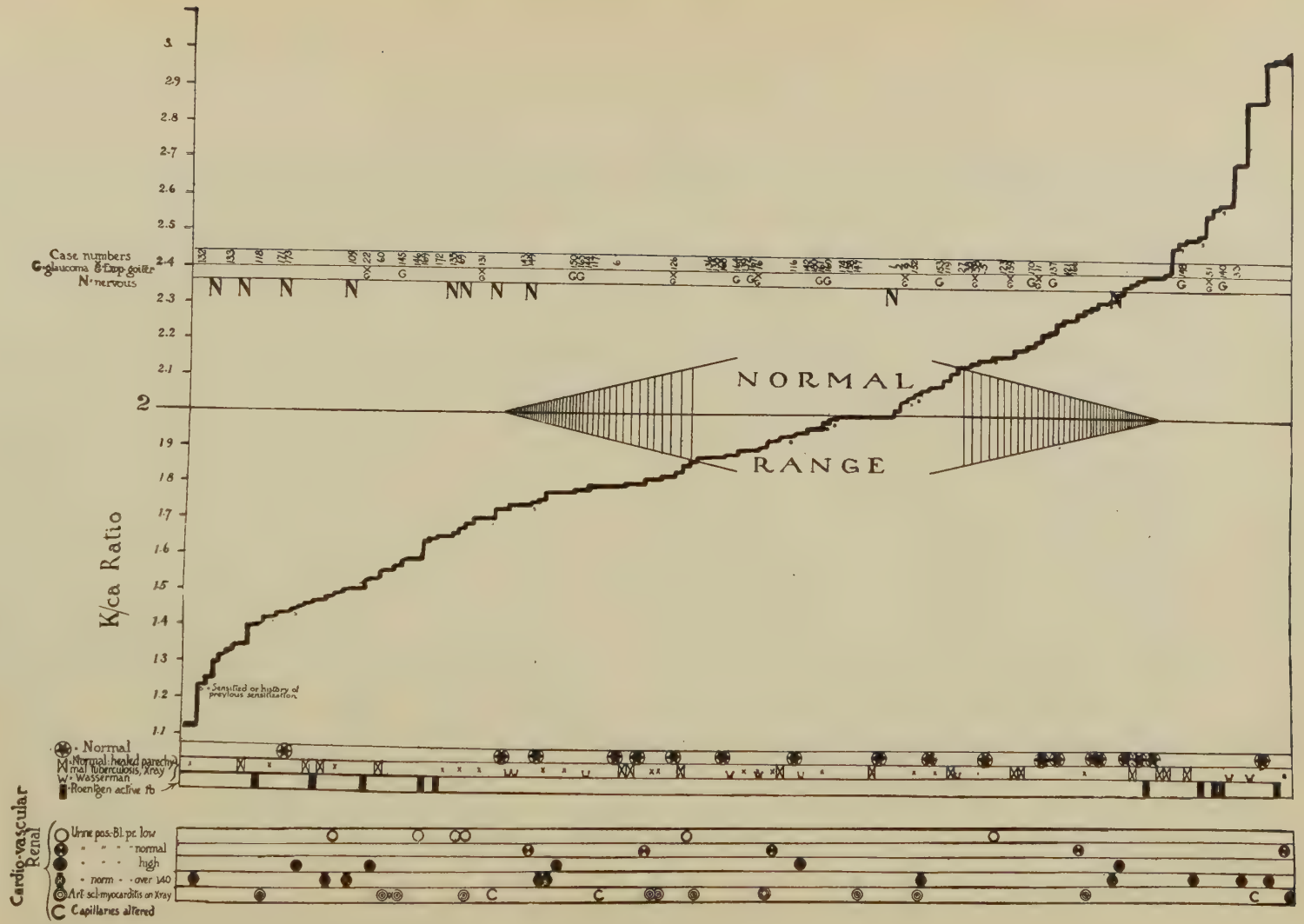

Chart 4.—The K/Ca ratio of normal persons and patients with various clinical conditions (indicated by heavy line). Individual identification marks at bottom are included in the group of 100 "normal" men.

but these are all in persons of advanced age. With one exception, the members of this group all have sthenic hearts.

"Nervous" Persons.—The so-called nervous group seems, without doubt, to be associated with changes in the K/Ca ratios. One must, however, consider the possibility that the changes in the ratios are secondary to the nervous conditions rather than the cause of these. Perhaps some of the symptoms (feeling of weakness, etc.) may be sought in an alteration of the salt balance. These cases include the following:

Case 86.—A former dentist, American, 50 years of age, had always been the most nervous one of his family. A sister had exophthalmic goiter. The patient had an attack of angioneurotic edema when a dental student. He used alcohol excessively. The death of a child precipitated a "breakdown." He lost his practice and his family, and became "down and out." He worked occasionally as a janitor.

It may be noticed that the sugar and the globulin were increased, the total protein was low, the muscle reactivity was increased and the reaction to epinephrine hydrochloride was vagotonic The weight/length ratio was diminished.

Case 90.—A mail sorter, 30 years of age, complained that since the year previously he got "rattled" easily and was nervous. He was extremely sensitive to venipuncture. The family history was negative. The patient reacted markedly to epinephrine with a tremor and a feeling of discomfort. The weight/length ratio was diminished. The intracutaneous reactions to morphine and epinephrine (the flare) were increased; those to thyroxin were diminished. The capillaries of the skin were reduced in number.

Case 173.—A highly successful and intelligent American business man, 40 years of age, with cord tumor, had suffered from incidental worry for two years. The family history was negative other than that the mother was nervous and died from tuberculosis.

The K/Ca ratio in December, 1927, was 1.57 (calcium, 13.5; potassium, 21.3). The K/Ca ratio in May, 1928, was 1.43 (calcium, 12.7; potassium, 18.17). The sugar was 80, the globulins were diminished, the skin resistance was low, the blood pressure was low and the pulse rate was high. The patient reacted strongly to epinephrine. The weight/length ratio was diminished. The intracutaneous reactions to epinephrine were increased; flares due to morphine, thyroxin and caffein were absent.

Case 3.—A highly intelligent Jewish chemist, 25 years of age, had been nervous for several years. The father suffered from Raynaud's disease.

The patient's reaction to epinephrine was vagotonic. The weight/length ratio was normal. The intracutaneous reactions to thyroxin and caffein (wheals and flares) were diminished.

Case 109.—An American spinster, 42 years of age, spent much of her time in bed because of "weakness." She had a unilateral ovariectomy fifteen years previously. She menstruated normally. She complained of palpation, nervousness, weakness and excessive perspiration. One sister had an exophthalmic goiter. The mother, 72 years of age, was nervous, with a blood pressure of 160.

The reaction to epinephrine was slightly sympatheticotonic, the weight/length ratio low (140), the skin reactions to ice and the Kromayer light faint and the intracutaneous reactions to thyroxin (flares) increased.

Case 135.—A Jewish tailor, 26 years of age, was nervous. The mother died of "shock" following an air raid during the war. The patient had lost 15 pounds (6.8 Kg.) during the last year. The reaction to epinephrine was vagotonic. The weight/length ratio was low. The urine showed granular casts. The capillaries of the skin showed granulations. A healed parenchymal tuberculosis was revealed by the x-rays. The globulins were increased. The pharmacologic skin reactions to epinephrine and morphine (wheals and flares) were reduced; the wheals due to thyroxin and caffein were increased, and the flares were absent.

Case 69.—A Jewish medical student, 22 years of age, alert and intelligent, had a duodenal ulcer and was nervous. He had an occasional tremor. His blood pressure was increased. The mother was nervous and had high blood pressure (210); the father was nervous and had high blood pressure (175). The patient felt weak when blood was drawn. He gave a marked reaction to epinephrine; he felt ill, had a headache and turned pale, and the vascular reaction was markedly sympatheticotonic. The weight/length ratio was low. The pharmacologic skin reactions to epinephrine and thyroxin (wheals and flares) were increased; the wheal due to caffein was increased.

Case 80.—An American electrician, 30 years of age, was nervous and had a tremor. He became nervous in 1924 after an explosion in a salt mine. He had urticaria in 1922.

The reaction to epinephrine was not marked. The reaction to the Kromayer light was marked and the capillary permeability was high. The resistance of the skin to electric current was high. The weight/length ratio was normal. All flares due to the pharmacologic substances employed in the intracutaneous injections were increased. The wheal due to epinephrine was diminished and that from thyroxin was increased. The capillaries of the skin showed beginning granulations.

Case 149.—An American plumber, 35 years of age, had had financial reverses, and was nervous and sleepless. The family history was negative, except for tuberculosis.

The reaction to epinephrine was not marked. The Kromeyer light erythema time was shortened, the skin resistance was high and the weight/length ratio was relatively low. The serum globulins were practically absent. The pharmacologic skin reactions to epinephrine were negative, the flares due to other intracutaneous injected substances were reduced or absent and the wheal due to thyroxin was increased.

Case 1.—A Jewish medical student, 23 years of age, who had a "nervous breakdown" a year before examination, felt weak and had a tremor.

The reaction to epinephrine was marked, the sugar was increased and the Kromayer light, ice and blister reactions were delayed. The weight/length ratio was low. The intracutaneous injection of epinephrine hydrochloride and morphine left the skin unchanged; the wheal and the flare due to thyroxin were increased.

Case 92.—A Jewish medical student, 23 years of age, was nervous and unable to concentrate, and had a feeling of weakness and an occasional tremor. He had bowel movements once or twice a week; he sweat easily. The father died from hypernephroma; the mother had periarteritis nodosa (?). The reaction to epinephrine was marked. The blister time and ice reaction were delayed. The

reaction to the Kromayer light was faint. The skin resistance was increased. The weight/length ratio was normal. The intracutaneous reactions to epinephrine and morphine were normal. Those to thyroxin were increased.

The K/Ca Ratio.—In one of our examinations of this material in its relation to the vascular reaction to epinephrine [8] it was found that a small group of outstandingly sympatheticotonic persons had low K/Ca ratios as compared with the vagotonic ones. We mentioned, however, that many exceptions were observed.

It is apparent that certain disturbances closely associated with a vascular supply are definitely associated with an alteration of the K/Ca ratio. These manifestations take the form of lesions of the skin, lesions of the gastro-intestinal tract, respiratory diseases (hay-fever, asthma, etc.), glaucoma, etc. A change of the K/Ca ratio may influence the permeability of the endothelial cells, which would result in instability and a probable tendency to sudden alterations producing not only edema but other local disturbances of cell function with pruritis, sclerosis, atrophy, etc. Such a change may also involve the contractile mechanism of the vessels including both capillary and arteriole and arterial elements, through the autonomic nervous supply.

It seems probable that the higher centers may play a rôle in this vegetative reorientation. Our results make it evident that the majority of the so-called nervous persons have a low ratio. In this change, the calcium is less involved than the potassium; the calcium may range from high to normal, but the potassium is usually found to be low.

We have the impression that this may result from mental disturbances. It is difficult, however, to determine whether mental disturbances precede the change in the chemical blood picture or follow as a result of it. Tómasson,[9] in a series of carefully conducted examinations of persons with psychic disturbances, found that the K/Ca ratio showed alterations before the onset of the mental upset. Certainly, a mere examination of the calcium is insufficient to supply us with the necessary information. In view of the close connection between the mental state and the functioning of certain of the endocrine glands, the change in the K/Ca ratio with change in the mental condition should not surprise us.

It seems probable that it is the abnormality of the ratio rather than its change in any one direction that brings about functional vascular disturbances and with this certain manifestations of disease. Thus, one

8. The Relation of the Reaction to Epinephrine to the Potassium/Calcium Ratio and to Other Ratios, Article IV, p. 121.

9. Tómasson, H.: Blodets Elektrolyter, etc., Copenhagen, Levin & Mungsgaard, 1927.

may examine the history of two persons who are, respectively, at the bottom and the top of the K/Ca scale.

Case 132.—A medical student, 26 years of age, alert and intelligent, had a K/Ca ratio of 1.12. He was the son of a physician. When 12 years of age, he had severe attacks of hyperacidity and dizziness with vomiting. These attacks would occur intermittently several times a month and usually lasted a day; they were relieved by food. The attacks became milder until 1918; then they became more severe. He was free from them at the time of examination. In 1919, he had a severe attack of hiccup, which lasted for forty-eight hours. From 1918 to 1921, he was bedridden with tuberculosis of the right lung. During the course of the tuberculosis, he suffered severely from night sweats. He had hay-fever from the time that he was a young boy until 1919, when it disappeared, and at various times in 1918 he suffered from urticaria. In 1920, he had influenza, associated with a mastoiditis. Since 1919, he had had ulcerative colitis with the possibility of a duodenal ulcer. For one week in 1919, he had diabetes insipidus. During the past three years, he had had hypo-acidity. At the time of examination he was apparently well, except for chronic eczema on both hands. Physical examination revealed no marked changes.

The x-ray picture of the chest was practically negative. However, he had an eosinophilia of from 10 per cent to 14 per cent, and stated that he had never been able to alkalinize the urine, despite large doses of bicarbonate.

Case 93.—An American laborer of Irish extraction, 53 years of age, rather alert, intelligent and somewhat irritable, had a K/Ca ratio of 3.2. He had always done heavy work. He was a periodic drinker until four years before. He had had hay-fever and asthma all of his life. He was attacked by these in the fall, and he stated that he was sensitive to ragweed. For the past fifteen years, he had been sensitive to halibut. X-ray examination revealed evidence of a myocarditis, and he complained of shortness of breath. The family history was apparently negative.

Calcium.—The lowest amount of serum calcium, 7.4 mg. per hundred cubic centimeters, occurs in a patient (no. 104) with roentgenologic evidence of active tuberculosis and a coincident high blood pressure; the largest amount, 14 mg. per hundred cubic centimeters, occurs in a patient with healed parenchymal tuberculosis. The actually normal group have a range of calcium values from 8.2 to 12.7 mg.

In Table 9, some of the observations on the twenty persons having the highest levels of calcium (averaging 12.7 mg. per hundred cubic centimeters) have been tabulated. The corresponding observations on the persons with outstandingly low levels of calcium are tabulated in table 10. In order to facilitate comparison, table 11 brings together the averages for the group with high levels of calcium, the group of 100 "normal" men and the group with low levels of calcium.

In chart 5, the normal ranges of the calcium levels are presented. The persons with healed tuberculosis are more frequently in the normal range or the high range, while those with roentgenologic evidence of active tuberculosis are scattered. There appears to be no correlation of these conditions with the cardiovascular condition.

TABLE 9.—*The Results of Examinations of the Twenty Persons with the Highest Levels of Serum Calcium*

Individual Number	Diagnosis	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure: Systolic	Blood Pressure: Diastolic	Pulse Rate	Permeability of Capillaries
18	Healed tuberculosis	58.4	70.2	2	1	10	Vagotonic	....	....	120	80	88	70
46	Inanition	56.2	61	2	1.70	15	Sympathetic-cotonic	21.2	12.2	140	82	76	59
132	Eczema	40.3	67	...	0.31	10	Vagotonic	18.4	13.6	132	78	56	68
133	Scleroderma	50.2	77	...	0.70	30	Sympathetic-cotonic	....	....	92	68	96	..
23	Healed tuberculosis	57.4	85	3	0.42	28	Vagotonic	17.2	7.2	105	58	82	67
172	Raynaud's disease	....	76	...	0.08	45	Sympathetic-cotonic	22.4	18	108	78	94	72
2	Epilepsy	55.6	74	...	0.10	..	Sympathetic-cotonic	....	....	100	68	100	69
173	Worry	55.7	80	...	0.09	15	Sympathetic-cotonic	21	18	106	68	92	57
17	Normal	59.1	61.5	6	0.22	20	Vagotonic	20.8	20.6	130	70	66	66
86	Nervous	55	94	1.4	0.36	25	Vagotonic	18.8	15.4	118	60	74	58
171	Urticaria	48.7	72	...	0.08	20	Sympathetic-cotonic	17.5	18	114	66	96	73
112	Arteriosclerosis	57	68	2.4	2.70	18	Vagotonic	22.4	9.8	139	80	75	54
169	Buerger's disease	55.1	67	...	0.23	25	Sympathetic-cotonic	20.8	18	118	78	82	62
62	Aortic regurgitation	56.8	67	5	0.15	15	Vagotonic	17.2	11.4	140	40	64	52
118	Chronic arthritis; pleurisy	54.2	80	2.8	1.90	12	Vagotonic	16.8	12	120	60	72	87
127	Nephritis	59.1	81	3	1.20	16	Sympathetic-cotonic	18.4	15.4	106	76	86	50
110	Healed tuberculosis	57.2	61	2	0.60	30	Vagotonic	20.8	12	110	62	84	54
22	Exophthalmic goiter	52	91	3	0.17	5	Sympathetic-cotonic	26.4	5	144	74	92	73
15	Healed tuberculosis	57.6	70	6	0.19	38	Sympathetic-cotonic	23.2	11.6	128	68	60	68
1	Nervous	62.1	113	...	0.11	25	Sympathetic-cotonic	20	13.2	132	74	80	68
Averages and totals		55.2	75.7	3.2	0.61	21	9 V., 11 S.	20.2	13.6	120	69	80	64

TABLE 10.—*The Results of Examinations of the Twenty Persons with the Lowest Levels of Serum Calcium*

Individual Number	Diagnosis	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure: Systolic	Blood Pressure: Diastolic	Pulse Rate	Permeability of Capillaries
104	Tuberculosis; arteriosclerosis	57.2	55	1.2	0.08	25	Vagotonic	20.8	12	176	100	84	54
93	Myocarditis; hay-fever	57	70	2.4	0.25	12	Vagotonic	20.4	10	113	71	86	50
61	Arteriosclerosis	53.1	72	7.4	0.28	7	Vagotonic	19.6	13.4	142	82	64	70
95	Healed tuberculosis	61.6	77	1.6	0.39	10	Sympathetic-cotonic	23.6	12	110	66	68	59
115	Arteriosclerosis	51.8	60	2	0.28	10	Vagotonic	17.2	14.2	148	84	84	46
55	Nephritis	56.6	73	0.6	0.38	20	Vagotonic	17.6	11.2	128	68	84	60
80	Nervous	53.2	69	3.8	1.6	30	Vagotonic	14.8	13.4	116	68	64	91
114	Tuberculosis	60.6	75	4	0.14	25	Sympathetic-cotonic	20.4	12	174	60	48	64
107	Myocarditis; arteriosclerosis	55.2	60	2.8	0.33	15	Vagotonic	20.8	13.4	134	72	72	58
137	Glaucoma	51.9	73	0.8	1.90	30	Vagotonic	15.4	13	119	67	78	61
83	Normal	53.1	68	4	0.16	20	Vagotonic	17.2	13.4	114	64	60	51
96	Arteriosclerosis	53.4	77	1.6	0.11	40	Vagotonic	18	12.4	140	85	68	57
159	Exophthalmic goiter	54.8	71	...	0.22	7	Sympathetic-cotonic	25	12	132	68	76	69
81	Myocarditis; arteriosclerosis	57	63	2.3	0.10	45	Vagotonic	14	10	144	63	76	59
97	Normal	57.2	60	4.5	0.22	20	Sympathetic-cotonic	19.2	12	100	62	68	54
92	Nervous	56.8	67	2.9	0.57	20	Sympathetic-cotonic	20.4	15.2	110	60	72	82
87	Normal	55.4	94	3.5	0.42	18	Sympathetic-cotonic	16	12	104	62	70	56
78	Normal	62.7	67	1	0.62	10	Sympathetic-cotonic	19.6	12.4	122	70	74	86
35	Normal	57.6	79	1.8	0.38	20	Vagotonic	22.8	9.2	108	78	62	54
164	Syphilis; glaucoma	55.6	65	...	0.23	15	Vagotonic	18	....	110	75	80	71
Averages and totals		56.1	69.7	2.6	0.43	19.3	13 V., 7 S.	19	12.3	127	71	82	62.6

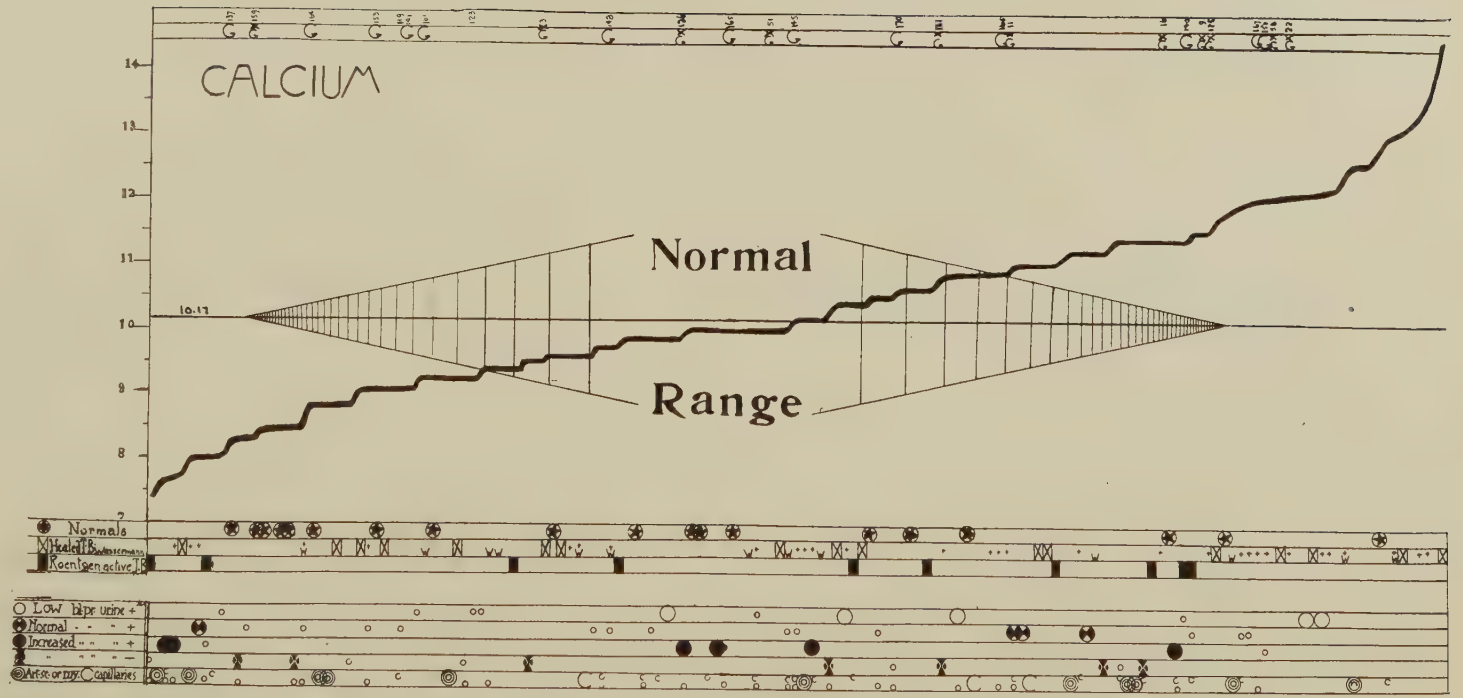

Chart 5.—The calcium level in the serum of normal persons and patients with various clinical conditions.

The groups with high levels of calcium include none of the persons having active tuberculosis, but include a number of persons with skin disorders, as well as those with peripheral vascular changes—scleroderma, Raynaud's disease, Buerger's disease, etc. A number of outstandingly sympatheticotonic persons are included, but vagotonic types also occur.

In general, the carbon dioxide tension is reduced; the sugar, the skin resistance, the pulse rate, the wheals due to epinephrine and thyroxin and the permeability of the capillaries are increased; the ice reaction time is prolonged, and the blood pressure is lower than in the group with low levels of calcium.

The group with low levels of calcium, on the other hand, includes two persons with active tuberculosis, an increased number of arterio-

TABLE 11.—*Comparison of the Averages Obtained for the Groups Showing High Levels and Low Levels of Calcium with the Averages Obtained for the Group of One Hundred Normal Men*

Group	Number in Group	Calcium, Mg.	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Pulse Rate	Ice Reaction Time, Seconds	Intracutaneous Reaction to: Epinephrine, Wheal (Diameter, Mm.)	Intracutaneous Reaction to: Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure: Systolic	Blood Pressure: Diastolic	Permeability of Capillaries
Group with high level of calcium	20	12.7	55.2	75.7	3.2	0.61	80	21	20.2	13.6	120	69	64
Group of "normal" men	100	10.17	57.7	71	3.2	0.46	72	19	19.2	11.2	124	71	62
Group with low level of calcium	20	8.1	56.1	69.7	2.6	0.43	72	19.3	19	12.3	127	71	62.6

sclerotic persons (as proved by roentgen examination), as well as more normal persons. There are, too, apparently more persons of the vagotonic type in this group, thirteen of the twenty giving such a reaction.

Potassium.—The highest potassium value, 29.7 mg. per hundred cubic centimeters, is found in a patient with glaucoma, hay-fever and roentgenologic evidence of active tuberculosis; the lowest 13.1 in a person with roentgenologic evidence of active tuberculosis. The range for the actually normal group is from 16.6 to 27.4.

In tables 12, 13 and 14, some of the observations on the group with high levels of potassium (averaging 26.5) are recorded. In table 13, the corresponding observations on the group with low levels of potassium (averaging 15.1) are recorded. For purposes of comparison, table 14 brings together the averages of the groups with the high levels of potassium, the group of 100 "normal" men and the group with low levels of potassium.

TABLE 12.—*Results of Examinations of the Twenty Persons with the Highest Levels of Potassium*

Individual Number Diagnosis	Potassium, Mg.	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Thyroxin, Wheal (Diameter, Mm.)	Epinephrine, Wheal (Diameter, Mm.)	Blood Pressure: Systolic	Blood Pressure: Diastolic	Permeability of Capillaries	Inflammatory Index
140 Glaucoma; tuberculosis; sensitized	29.7	55.6	82	...	0.45	40	Vagotonic	18	27	100	70	68	4
25 Tuberculosis.....	28.8	59.8	67	1.2	0.24	20	Sympathetic-otonic	21.2	9	140	80	57	9.5
23 Healed tuberculosis	28.6	57.4	85	3	0.42	28	Vagotonic	17.2	7.2	102	58	67	11.1
56 Tuberculosis.....	28.6	56.6	65	1	0.32	15	Vagotonic	17.2	13.4	124	88	61	10
141 Glaucoma.....	28.2	64.6	86	...	0.20	15	Vagotonic	17.4	10	118	78	..	....
34 Changes in capillaries	27.7	56.4	78	2.7	0.59	25	Vagotonic	18	7.2	134	78	56	7.7
48 Syphilis.....	27.6	58.3	71	1.6	0.10	35	Sympathetic-otonic	19.2	8	104	72	66	9.7
50 Normal.....	27.4	64.9	..	2.8	0.48	15	Sympathetic-otonic	24.8	10.4	128	70	71	8.8
26 Syphilis.....	26.6	63.4	69	2	0.28	35	Vagotonic	19.6	7.2	92	48	72	11
36 Albuminuria.....	26.3	57.6	90	2.8	0.11	20	Vagotonic	20.8	7.4	104	50	58	7.2
47 Healed tuberculosis	26.2	56.4	72	5	0.13	15	Vagotonic	21.6	9	136	64	62	12.8
32 Arteriosclerosis.....	26.1	54.1	76	7.4	0.18	25	Vagotonic	23.6	9.8	144	86	60	10
33 Epilepsy.....	26.1	54.5	83	2	1.75	12	Sympathetic-otonic	20	5.4	122	66	73	10
2 Epilepsy.....	26.1	55.6	74	...	0.10	..	Sympathetic-otonic	....	....	100	68	69	9.8
58 Exophthalmic goiter	25.9	52.9	120	...	0.10	26	Vagotonic	19.6	11.2	124	60	75	15
81 Arteriosclerosis; myocarditis	25.8	57	63	2.3	0.10	45	Vagotonic	14	10	144	63	59	10
51 Exophthalmic goiter	25.8	55.5	91	5	0.13	..	Sympathetic-otonic	19.2	9.2	124	50	77	14
5 Nervous.....	25.7	63.9	72	3.2	0.21	..	Vagotonic	....	....	132	92	72	13
21 Arteriosclerosis.....	25.6	62.9	72	3.9	0.74	25	Vagotonic	23.2	7.2	140	84	62	9
35 Normal.....	25.2	57.6	79	1.8	0.38	20	Vagotonic	22.8	9.2	108	78	54	6.7
Averages and totals...	26.5	58	75	2.9	0.35	24	14 V., 6 S.	20	9.8	121	70	65	10

TABLE 13.—*The Results of Examinations of the Twenty Persons with the Lowest Levels of Potassium*

Individual Number Diagnosis	Potassium, Mg.	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure: Systolic	Blood Pressure: Diastolic	Permeability of Capillaries	Inflammatory Index
88 Tuberculosis.....	13.1	58.1	79	2.5	0.68	15	Vagotonic	18.4	12.4	128	76	58	8.1
80 Nervous.....	13.7	58.2	69	3.8	1.60	30	Vagotonic	14.8	13.4	116	68	91	15.1
146 Myasthenia gravis.	14.4	71.06	77	...	0.55	30	Vagotonic	18	19	120	78	75	5
90 Nervous.....	14.5	57.9	68	...	0.44	10	Sympathetic-otonic	18.4	6.2	122	54	69	7.6
132 Eczema.....	15	40.3	67	...	0.31	10	Vagotonic	18.4	13.4	132	78	68	11.3
62 Aortic regurgitation	15.2	56.8	67	5	0.15	15	Vagotonic	17.2	11.4	140	40	52	8.7
115 Arteriosclerosis.....	15.2	51.8	60	2	0.28	10	Vagotonic	17.2	14.2	148	84	46	5.7
108 Tuberculosis.....	15.3	54.1	63	0.6	0.44	18	Sympathetic-otonic	18	14.8	94	52	63	8
134 Arteriosclerosis.....	15.4	54.8	71	...	0.68	12	Sympathetic-otonic	23.6	19.2	148	86	60	4
130 Nephritis.....	15.5	55.6	86	2	0.35	15	.....	20	11.2	106	..	71	4.7
77 Sensitized.....	15.6	60.6	71	1	1	35	Vagotonic	14	10	126	78	87	10
145 Glaucoma.....	15.7	55.4	70	...	0.35	20	Sympathetic-otonic	18	16	136	80	67	4.4
86 Nervous.....	15.9	55	94	1.4	0.36	25	Vagotonic	18.8	15.4	118	60	58	3.8
69 Nervous.....	16	54.8	70	2	1.90	20	Sympathetic-otonic	21.2	14.4	140	48	51	12.7
109 Nervous.....	16.1	51.4	67	...	0.47	25	Vagotonic	18	12	106	70	72	12
127 Nephritis.....	16.2	59.1	81	3	1.20	16	Sympathetic-otonic	18.4	15.4	106	76	50	3.8
110 Healed tuberculosis	16.3	57.2	61	2	0.60	30	Vagotonic	20.8	12	110	62	54	7.2
65 Nephritis.....	16.4	58.1	65	0.4	0.80	13	Sympathetic-otonic	15.8	9.2	100	70	61	10
64 Normal (nervous)..	16.6	55	52	5	0.22	7	Sympathetic-otonic	20	6.4	112	60	66	10
45 Arteriosclerosis.....	16.6	54.3	77	7.4	0.28	20	Vagotonic	20.4	16.4	162	114	54	9
Averages and totals...	15.1	55.2	70	2.7	0.63	18.5	11 V., 8 S.	18.4	13.1	123	70	63	8

In the group with the higher levels are three patients with roentgenologic evidence of active tuberculosis, two with syphilis, two with glaucoma and two with epilepsy. The reaction to epinephrine is predominantly vagotonic. The group with the low levels includes the "nervous" persons. In this group eleven react vagotonically.

As compared with the group having low levels of potassium the group having the high levels reveals higher Co_2 combining power, more sugar, larger wheals due to epinephrine, smaller wheals due to thyroxin and a higher inflammatory index. The reaction to ice is delayed.

TABLE 14.—*Comparison of the Averages Found for the Groups with High and Low Levels of Potassium with the Averages Found for the Group of One Hundred "Normal" Men*

	Number in Group	Potassium, Mg.	Carbon Dioxide Combining Power	Sugar, Mg.	Muscle Reaction	Skin Resistance	Ice Reaction Time, Seconds	Vascular Reaction to Epinephrine	Epinephrine, Wheal (Diameter, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Blood Pressure: Systolic	Blood Pressure: Diastolic	Permeability of Capillaries	Inflammatory Index
Group with high level of potassium	20	26.5	58	75	2.9	0.35	24	14.2	20	9.8	121	70	65	10
Group of "normal" men.....	100	20.4	57.7	71	3.2	0.46	19	....	19.2	11.2	124	71	62	8.2
Group with low level of potassium	20	15.1	55.2	70	2.7	0.63	18.5	11.2	18.4	13.1	123	70	63	8

SUMMARY AND CONCLUSIONS

An examination was made of the serum calcium and potassium of 100 so-called normal persons. Of this group, twenty were regarded as actually normal on careful examination.

The K/Ca ratio from 1.7 to 2.4 we regard as normal. Persons with roentgenologic evidence of active tuberculosis are at the extreme ends of the scale. Those with vascular changes in addition to the tuberculosis have the higher ratios. Among abnormal persons, glaucoma and exophthalmic goiter produce no marked deviations from normal. "Nervous" persons have low ratios.

The normal calcium range was found to be from 8.2 to 12.7. In the group with the high range are the persons with diseases of the skin, as well as those with peripheral vascular disturbances, such as scleroderma, Buerger's disease, Raynaud's disease, etc. These persons tend toward the sympatheticotonic type.

The normal potassium range extended from 16.6 to 27.4. The group with low levels of potassium includes the "nervous" persons.

TOTAL PROTEINS

Serum proteins for the normal as well as abnormal groups varied from a low of 6.33 per cent in patient 86 (nervous) to a high reading of 9.87 per cent in a case of so-called Buerger's disease (syphilitic). For the strictly normal group, the range was from 7.5 to 8.5 per cent. Patient 17, classified as normal, but with an abnormal K/Ca ratio, etc.,

TABLE 15.—*The Results of Examinations of the Twenty Persons with the Lowest Concentrations of Protein*

Individual Number	Protein, Mg.	Diagnosis	CO_2 Combining Power	Weight/ Length Ratio	Basal Metabolic Rate
86	6.33	Nervous	55	176	6.4
145	6.55	Glaucoma; syphilis	55.4	166	19
85	6.65	Fever, unknown origin	56.9	187	18.8
140	6.77	Tuberculosis; glaucoma	55.6	...	....
60	6.87	Cardiovascular renal condition	56.6	229	....
116	7	Urticaria	66.1	195	9
67	7	Dwarf	56.9	195	32
118	7	Tuberculosis; arthritis	54.2	154	—11
77	7	Sensitized	60.6	187	7.9
30	7.07	Arteriosclerosis	62.5	175	—6
139	7.10	Urticaria	50	176	5
123	7.16	Carcinoma of thyroid	52.4	263	48
110	7.20	Healed tuberculosis	57.2	190	49
11	7.20	Exophthalmic goiter	58.1	195	42
24	7.20	Healed tuberculosis	53.7	219	1
101	7.20	Eczema	57.4	191	31
92	7.20	Nervous	56.8	210	—1
96	7.26	Cardiovascular renal condition	53.4	243	31
132	7.30	Eczema	40.3	234	—1.2
161	7.30	Glaucoma	49.4	171	+16

TABLE 16.—*The Results of Examinations of the Twenty Persons with the Highest Concentrations of Protein*

Individual Number	Protein, Mg.	Diagnosis	CO_2 Combining Power	Weight/ Length Ratio	Basal Metabolic Rate
169	9.87	Buerger's disease	55.1	...	+7
164	9.56	Glaucoma; syphilis	55.6	223	—4.7
136	9.28	Pellagra	57.9	180	20
75	9.23	Cardiovascular renal condition	61.6	243	+2.5
56	9.14	Tuberculosis	56.6	247	—17.9
125	9.13	Exophthalmic goiter	56.5	197	59
170	8.92	Glaucoma	52.5	170	+33
5	8.92	Neurosis	6.39	210	....
32	8.80	Cardiovascular renal condition	54.1	190	+22
146	8.80	Myasthenia	71.06	192	+ 1.8
79	7.87	Ulcer	57	220	—15.2
17	8.72	Normal (?)	59.1	216	—11
167	8.71	Glaucoma; arteriosclerosis	47.9	158	—13
117	8.71	Arthritis; syphilis	52.4	195	— 7
40	8.71	Changes in capillaries	55.7	201	22
154	8.71	Glaucoma	56.6	181	18
10	8.70	Healed tuberculosis	59.4	230	—12.4
68	8.66	Healed tuberculosis	51.1	217	25.8
121	8.66	Arthritis deformans	56.8	294	11
66	8.66	Cardiovascular renal condition	53.1	257	1.3

is again unusual in having a somewhat higher protein concentration, 8.75 per cent. We do not regard this as normal. The twenty persons with the lowest concentrations of the entire series are tabulated in table 15 (average, 7 per cent).

The twenty persons with the highest concentrations are presented in table 16 (average 8.9).

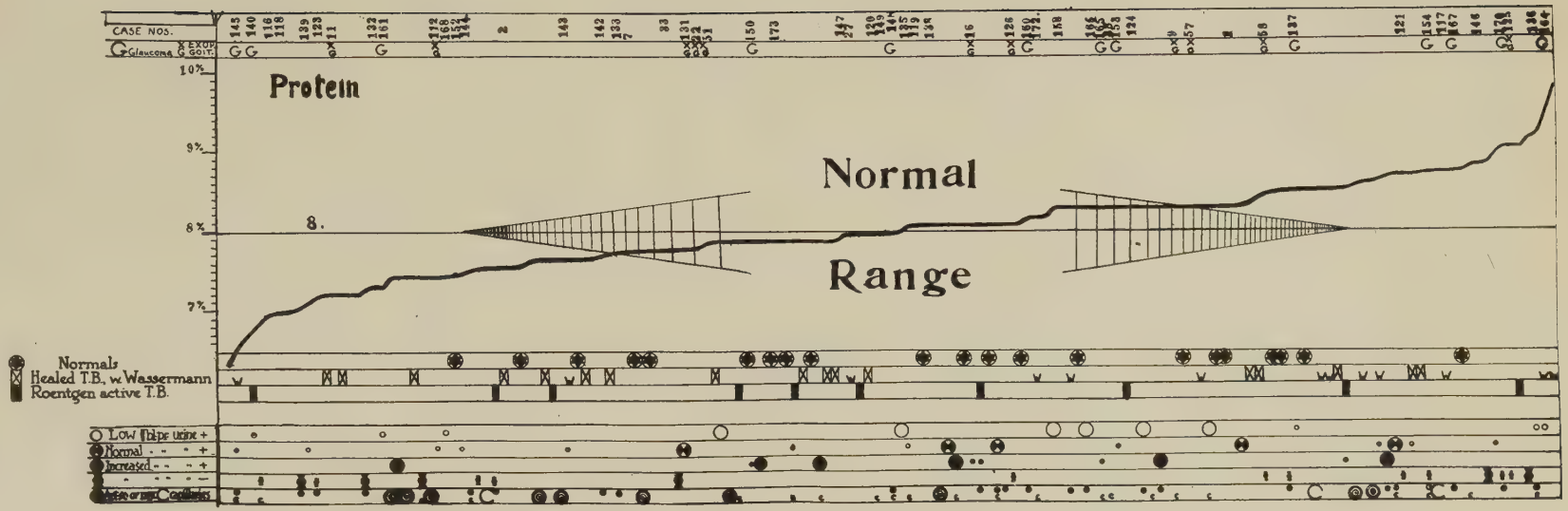

Chart 6.—The amount of protein in the serum of normal persons and patients with various clinical conditions.

A table of comparison with the normal is given in table 17. There are no obvious correlations other than those indicated, and these are by no means striking. A graphic presentation has been prepared in chart 6.

TABLE 17.—*Comparison of the Averages Found for the Groups with High and Low Concentrations of Protein with Those Found for the One Hundred "Normal" Men*

Group	CO_2 Combining Power	Weight/ Length Ratio	Basal Metabolic Rate
Group with low level of protein	54.8	197	+15
Group of 100 "normal" men	57.7	217	+ 8
Group with high level of protein	57.1	210	+ 6

In general it will be observed that in the group of 100 "normal" persons, both active and inactive tuberculosis revealed by the x-rays is scattered over the entire range. The cases in which there were cardiovascular renal disturbances more frequently showed the higher concentrations. This is true of the cases in which glaucoma is present as well.

GLOBULINS

The range of globulins for the entire series is from 0 to 90 per cent. For the actually normal persons, the range is approximately from 20 to 45 per cent (with an albumin/globulin ratio of from 5 to 1.2). It may be noted from the curve in chart 7 that two normal persons (nos. 17

TABLE 18.—*The Results of Examinations of the Twenty Persons with the Lowest Amounts of Globulin*

Individual Number	Globulin	Diagnosis	Reaction to Epinephrine		Reaction to Thyroxin	
			Wheal, Diameter, Mm.	Flare, Radius, Mm.	Wheal, Diameter, Mm.	Flare, Radius, Mm.
149	0	Nervous	20	9.7	19	0
153	0	Edema; glaucoma; nephritis	22	6.5	18	0
144	2	Arteriosclerosis; pellagra; changes in capillaries	14.4	11.5	15	0
154	3	Arteriosclerosis; glaucoma; changes in capillaries	23	10	26	0
173	6	Cord tumor	21	12.5	18	0
166	8	Eosinophilia	17	11.5	18	0
138	11	Fröhlich's syndrome (?)	23	9.5	17	6.5
168	13	Orthostatic albuminuria	18	16	14	0
150	15	Glaucoma	17	14	16	0
165	16	Glaucoma	16.8	13	12.5	0
17	17	Normal	20.6	10.2	20.6	10.4
49	17	Cardiovascular renal condition	12.4	10.2	4.2	1
158	17	Hodgkin's disease	19.2	11.3	28	0
59	17	Normal	22	7.2	15.6	8
139	18	Urticaria	16	11	14	12.5
25	19	Tuberculosis (x-ray evidence)	21.2	12.2	9	15.2
142	19	Tumor of the brain	18.6	8.7	17	0
169	20	Buerger's disease	20.8	11	18	0
164	20	Glaucoma	18	14.7		
21	20	Cardiovascular renal condition	23.2	12.6	7.2	2.6

and 59) are slightly below and three (nos. 41, 29 and 43) are at the upper margin. Of these persons, no. 17 has been noted previously because of his deviations; of the three with high globulin, no. 29 has a trace of bile in the urine and no. 43 a decrease in the number of the capillaries of the skin.

TABLE 19.—*The Results of Examinations of the Twenty Persons with the Highest Amounts of Globulin*

Individual Number	Globulin	Diagnosis	Reaction to Epinephrine: Wheal, Diameter, Mm.	Reaction to Epinephrine: Flare, Radius, Mm.	Reaction to Thyroxin: Wheal, Diameter, Mm.
133	90	Scleroderma	....	....	....
115	60	Cardiovascular renal condition	17.2	6.2	14.2
130	60	Cardiovascular renal condition; arteriosclerosis	20	5.4	14.2
24	60	Healed tuberculosis	16.8	12.6	6.6
102	55	Tuberculosis	23.2	7.4	12.2
128	55	Cardiovascular renal condition; sensitized	....	....	14.4
145	55	Glaucoma; Wassermann reaction +	18	13.6	16
27	52	Lead poisoning; Wassermann reaction +	....	....	....
42	50	Cardiovascular renal condition; myocarditis	19.2	11.8	9.2
43	50	Normal	22	7.4	10
108	50	Tuberculosis	18	2.4	14.8
84	50	Cardiovascular renal condition	16.4	8.4	10.1
120	50	Purpura	21.2	7.2	12.1
29	50	Normal	22.8	9.8	7.2
41	50	Normal	24	13.2	6.2
79	50	Ulcer	19.2	9.4	8.2
101	45	Sensitized	19.6	7	10
104	45	Tuberculosis	20.8	6.2	12
33	45	Epileptic	20	12.6	5.4
100	45	Healed tuberculosis	18.8	8.6	12

TABLE 20.—*A Comparison of the Averages Obtained for the Groups Showing Low and High Values of Globulin*

Group	Globulin, %	Reaction to Epinephrine: Wheal, Diameter, Mm.	Reaction to Epinephrine: Flare, Radius, Mm.	Reaction to Thyroxin: Wheal, Diameter, Mm.
Group with low level of globulin	12	19.2	11.3	16
Group with high level of globulin	50	18.7	8.3	10.6

In chart 7, it may be observed that the persons with cardiovascular renal lesions tend to accumulate at the high end of the scale of the globulin, as do the patients with active tuberculosis.

In table 18, we have tabulated the results of some examinations of the twenty persons with the lowest values of globulin and in table 19 of those with the highest values. In the latter group, it is of interest to note that the patient with generalized scleroderma had the highest amount.

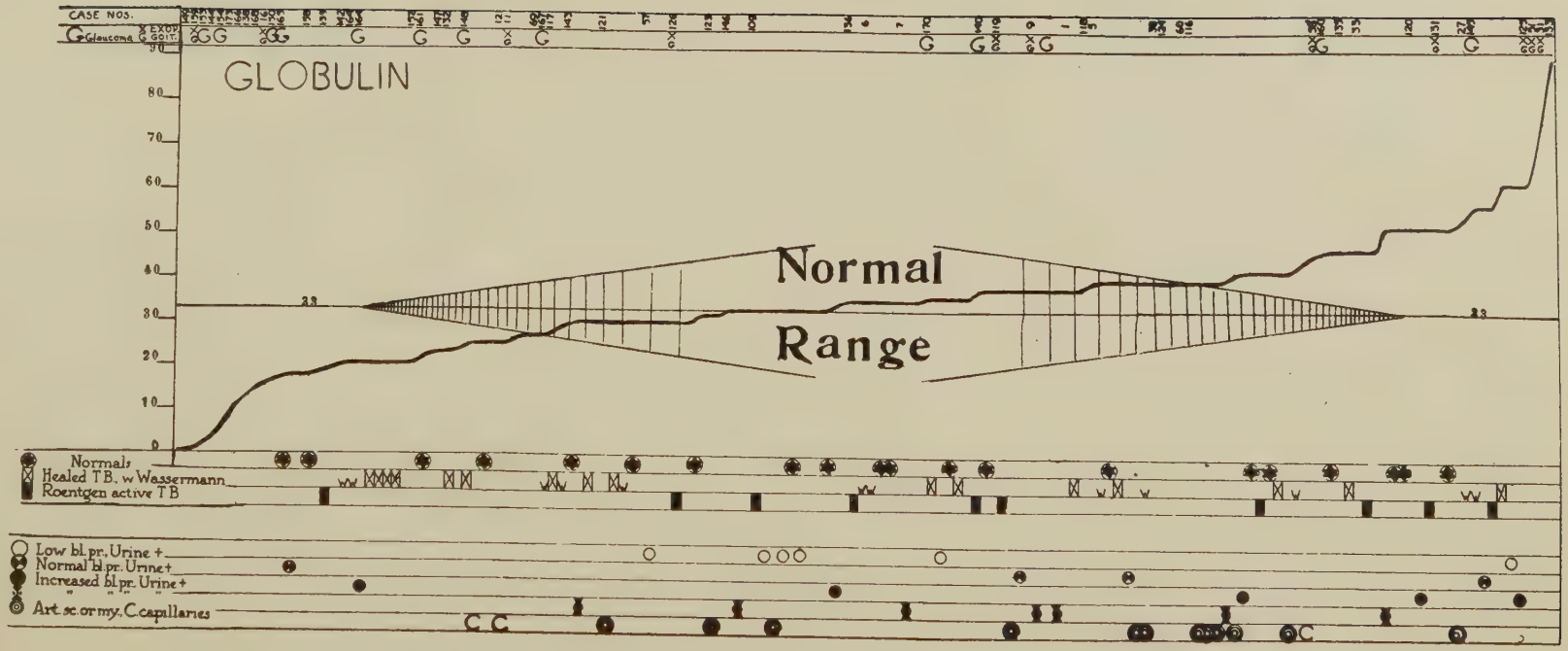

Chart 7.—The amount of globulin in the serum of normal persons and patients with various clinical conditions.

KROMAYER ERYTHEMA TIME

When the skin of the forearm is exposed directly to the light of the Kromayer lamp for thirty seconds, and the time from the beginning of the exposure to the appearance of the erythema determined, a considerable variation in the time, as well as in the intensity of the response, is found.

TABLE 21.—*The Results of Examinations of the Twenty Persons Showing the Most Rapid Reactions to Kromayer Light*

Individual Number	Diagnosis	Blister Time, Hr.	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Thyroxin, Wheal, Mm.	Pigmentation of Skin*	Color of Hair	Kromayer Light Erythema Time, Hr.	CO_2 Combining Power
45	Cardiovascular renal condition	6	54	9	20	Vagotonic	20.4	16.4	5	Dark brown	3/4	54.3
116	Urticaria	3.5	60	17	9	Vagotonic	20.4	5	4	Brown	1/2	55.1
66	Cardiovascular renal condition; arteriosclerosis; myocarditis	6	78	13	1.3	Sympathetic-otonic	20	10.2	3.5	Light brown	5/6	53.1
33	Epilepsy	7.5	73	10	—18	Sympathetic-otonic	20	5.4	3	Dark brown	1	54.5
100	Healed tuberculosis	6	53	9	—1.6	Vagotonic	18.8	12	3	Blond	1	58.3
152	Angioneuritic edema; sensitized	4	73	18	4.8	Vagotonic	26	9	3	Dark brown	1	63.4
158	Hodgkin's disease	15	61	4	+37	Sympathetic-otonic	19.2	28	...	Dark brown	1	57.8
142	Tumor of the brain	7	54	7.7	+05	Sympathetic-otonic	18.6	17	5	Dark brown	1	59
168	Orthostatic albuminuria	6	75	12	—9	Vagotonic	18	14	...	Brown	1	55.6
117	Syphilitic arthritis	6	61	10	—7	Sympathetic-otonic	19.2	20	5	Dark brown	1	52.4
60	Cardiovascular renal condition	8	..	....	0	Sympathetic-otonic	19.2	21	4.5	Light brown	1	56.6
149	Nervous	10	54	5.4	+5	Vagotonic	20	19	4	Dark brown	1	65.4
7	Cardiovascular renal condition	6	70	11.6	+7	Vagotonic	19.2	15.4	4.5	Light brown	1 11/10	57.9
46	Inanition	6	59	10	+13	Sympathetic-otonic	21.2	12.2	...	.....	1 1/6	56.2
160	Asthma; glaucoma	15	66	4.4	+16	Vagotonic	16	20	...	.....	1 1/6	62.7
112	Cardiovascular renal condition	6	54	9	+19.6	Vagotonic	22.4	9.8	4	Dark brown	1 1/6	59
111	Cardiovascular renal condition	6	57	9.5	+31	Sympathetic-otonic	22	10.8	5	Dark brown	1 1/6	55.3
120	Purpura	6	82	13	—5	Sympathetic-otonic	21.2	12.1	...	.....	1 1/5	52.2
48	Syphilis	6.75	66	9.7	+8	Sympathetic-otonic	19.2	8	...	.....	1 1/4	58.3
32	Cardiovascular renal condition	6	60	10	+22	Vagotonic	23.6	9.8	3.5	Brown	1 1/4	54.1

* Indicated on a scale of 1 to 10, 1 being white and 10 "light negro."

Investigators have previously determined that in the white race, the reaction is influenced by, but does not wholly depend on, the degree of pigmentation of the skin. It is known that constitutional factors play a rôle, and in the most practical field, i. e., the treatment of tuberculosis by light, it is common knowledge that a patient who does not react promptly and with production of pigment usually is not benefited by irradiation.

TABLE 22.—*The Results of Examinations of the Twenty Persons with the Slowest Reactions to Kromayer Light*

Individual Number	Diagnosis	Blister Time, Hr.	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Thyroxin, Wheal, Mm.	Pigmentation of Skin	Color of Hair	Kromayer Light Erythema Time, Hr.	CO_2 Combining Power
133	Scleroderma.....	....	..	....	2	Sympathetic-cotonic	....	....	5	Black	Did not appear	50.2
34	Changes in capillaries	7.25	56	7.7	13.6	Vagotonic	18	7.2	3.5	Black	8	56.4
49	Cardiovascular renal condition	6	66	11	7.1	Sympathetic-cotonic	12.4	4.2	3.5	Dark brown	5½	59.1
1	Nervous.....	8	68	8.5	7	Sympathetic-cotonic	20	13.2	4	Brown	5	62.1
63	Cardiovascular renal condition; arteriosclerosis	7.5	71	9.4	0.65	Vagotonic	20	12.2	4	Dark brown	5	62.4
99	Healed tuberculosis..	9	73	8.1	—3	Vagotonic	20.4	12.2	3.5	Blond	4½	57.4
107	Myocarditis; arteriosclerosis; cardiovascular renal condition	9	58	6.4	—65	Vagotonic	20.8	13.4	4	Light brown	4	55.2
127	Cardiovascular renal condition	13	50	3.8	—35	Sympathetic-cotonic	18.4	15.4	6	Brown	4	59.1
77	Sensitized.....	9	87	10	+7.9	Vagotonic	14	10	3	Dark brown	4	60.6
79	Ulcer (cardiovascular renal condition)	15	86	5.7	—15.2	Sympathetic-cotonic	19.2	8.2	2.5	Black	4	57
128	Cardiovascular renal condition; sensitized	15	58	3.8	—18	Sympathetic-cotonic	....	14.4	6	Dark brown	4	58.1
110	Healed tuberculosis..	7.5	54	7.2	.....	Vagotonic	20.8	12	4	Blond	4	57.2
2	Epilepsy.....	7	69	9.8	—11	Sympathetic-cotonic	....	....	4	Blond	3½	55.6
78	Normal.....	7	86	12	—0.62	Sympathetic-cotonic	19.6	12.4	3.5	Light brown	3¼	62.7
18	Healed tuberculosis..	8	70	8.7	+4.2	Vagotonic	....	....	3	Brown	3¼	58.4
29	Normal (bile pigment in urine)	6.5	70	10.7	3.5	Sympathetic-cotonic	22.8	7.2	4.5	Dark brown	3¼	60.1
50	Normal.....	8	71	8.8	21	Sympathetic-cotonic	24.8	10.4	4	Light brown	3	64.9
85	Fever, unknown origin	6	56	9.3	+18.8	Vagotonic	17.2	14.2	2	Dark brown	3	56.9
75	Cardiovascular renal condition	9	60	6.6	+2.5	Vagotonic	20.4	10	5.5	Dark brown	3	61.6
65	Cardiovascular renal condition	6	61	10	+29	Sympathetic-cotonic	15.8	9.2	2.5	Blond	3	53.1

TABLE 23.—*A Comparison of the Averages Obtained for the Groups with Fast and Slow Kromayer Lamp Erythema Times with Those Obtained for the Group of One Hundred "Normal" Men*

Group	Kromayer Light Erythema Time, Hr.	Blister Time, Hr.	Permeability of Capillaries	Inflammatory Index	Basal Metabolic Rate	Epinephrine, Wheal, Mm.	Thyroxin, Wheal, Mm.	Pigmentation of Skin	CO_2 Combining Power
Group with short erythema time.....	1	7.1	65	10	+7	20	13.8	4	56
Group of 100 "normal" men.....	2	7.5	62	8.2	+8	19.2	11.2	.	57.7
Group with long erythema time.....	3	8.5	66	8.3	+3	19	10.9	4	58.4

In our series of cases, we have roughly estimated the pigment content of the skin in each case by comparing it with a series of filter papers stained with varying dilutions of Bismarck brown. A scale from 1 to 10 was used, 1 being white and 10 approximating the color of the skin of a light negro.

The color of the hair was noted as: blond, black, dark brown, light brown and brown.

During the course of our examination of 100 so-called normal persons, it was shown that the prolongation of the erythema time was associated with a longer blister time, a lowering of the inflammatory index, a low basal metabolic rate, high CO_2 combining power and a lessened wheal due to epinephrine.

When we examine the group of 100 and the clinical material, as well, we find that the shortest time (45 minutes) was noted in patient 45, a man 39 years of age, with a vagotonic reaction to epinephrine and a history of urticaria twenty years previously. His blood pressure is 162 systolic and 114 diastolic (when 4 years of age, he had scarlet fever with involvement of the kidneys). The pigmentation of the skin is 5, and the hair dark brown.

On the other hand, two persons did not react at all. One had scleroderma; the other had an exophthalmic goiter, and had a fairly dark skin (pigment 6) and dark brown hair.

Our truly normal group had a range of erythema time from 75 to 195 minutes.

We have grouped the twenty persons with the shortest erythema times (average 1 hour) in table 21; and we present the twenty with the longest erythema times in table 22. For purposes of comparison, in table 23, we include with the averages for these two groups the averages for the 100 so-called normal men.

It appears that pigmentation, as such, plays comparatively little rôle in the relative rapidity or delay in the appearance of the Kromayer light erythema. Other factors with which the inflammatory index seems associated are probably of more importance. The CO_2 combining power and the endocrine status, particularly a difference in the wheals due to thyroxin are, perhaps, concerned.

Blondness per se is not important. In the group showing delayed reactions, we find four blonds and in the group showing rapidity, none at all.

BASAL METABOLIC RATE

In the introduction, we pointed out that determinations of the basal metabolic rate on a group of nonhospitalized workmen without a possibility of recheck affords a most unsatisfactory examination. We were, however, forced to accept this condition for our group of 100 "normal" men. Our average of +8 is evidence of a lack of absolute rest,

TABLE 24.—*The Results of Examinations of the Twenty Persons with the Lowest Basal Metabolic Rates*

Individual Number	Basal Metabolic Rate	Diagnosis	Blister Time, Hr.	Permeability Ratio	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Kromayer Light Erythema Time, Min.	Skin Resistance	Pulse Rate	Epinephrine, Pulse Pressure, % Increase	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Weight/Length Ratio
37*	—24.4	Normal	9	56	10	22.6	2.26	90	0.34	84	— 8	Vagotonic	20.4	21.6	10	0	254
13*	—22	Healed tuberculosis	8	64	9.6	23.8	2.48	150	0.89	72	+24	Sympatheticotonic	17.6	6.8	22.6	9.2	223
33	—18	Epilepsy	7.5	73	9.5	26.1	2.73	60	1.75	76	+ 2	Sympatheticotonic	20	12.6	5.4	0	240
128*	—18	Cardiovascular renal condition	15	58	10.2	19.7	1.93	240	1	84	+13	Sympatheticotonic	....	....	14.4	0	180
56*	—18	Tuberculosis	6	61	9.8	28.6	2.52	135	0.32	80	+14	Vagotonic	17.2	5.8	13	7.1	247
79*	—15.2	Ulcer	15	86	11.2	20	1.78	240	0.71	76	+ 8	Sympatheticotonic	19.2	9.4	8.2	12.2	220
167	—13	Glaucoma	15	56	12	22.7	1.9	120	0.85	84	+62	Sympatheticotonic	17	14.2	15	0	158
118	—11	Tuberculosis (?); arthritis	10	87	12.2	17.2	1.4	110	1.9	72	— 8	Vagotonic	16.8	7.4	12	8.6	154
17*	—11	Normal	8	66	12.7	18.2	1.43	90	0.22	66	0	Vagotonic	20.8	10.2	20.6	10.4	216
2	—11	Epilepsy	7	69	12.9	26.1	2.02	210	0.1	100	+64	Sympatheticotonic	....	....	....	....	...
168	— 9	Orthostatic albuminuria	6	75	9.40	17.6	1.88	60	0.16	80	+ 4	Vagotonic	18	16	14	0	215
96*	— 8	Nervous	9	69	11.4	14.5	1.34	105	0.44	67	+17	Sympatheticotonic	18.4	11.6	6.2	0	192
8*	— 8	Normal	10	64	10.5	21	2	120	0.48	60	+90	Sympatheticotonic	20.4	9.8	14	0	197
122*	— 7.3	Normal	4	68	10.6	19.2	1.81	...	0.37	68	— 3	Vagotonic	20	7.8	12	9	189
166	— 7	Eosinophilia	7	57	9.1	20.66	2.27	75	0.08	96	— 0	Vagotonic	17	11.5	18	0	200
117	— 7	Syphilitic arthritis	6	61	9.2	17.5	1.8	60	0.25	78	6	Sympatheticotonic	19.2	6.2	20	0	195
83*	— 7	Normal	9	51	8.2	19	2.31	90	0.16	60	+10	Vagotonic	17.2	9.2	13.4	11	258
106*	— 6.6	Cardiovascular renal condition	6	71	11.2	19	1.69	90	0.63	84	— 2	Vagotonic	19.6	7	11.2	0	243
3*	— 6.5	Healed tuberculosis	6.5	67	11.1	16.7	1.47	90	0.33	65	+ 8	Vagotonic	19.6	12.2	6.4	0	224
107*	— 6.5	Cardiovascular renal condition	9	58	8.1	18.4	2.3	255	0.33	72	— 1	Vagotonic	20.8	5.8	13.4	6.2	265
	11.72	Averages and totals	8.65	65.8	10.44	20.4	1.98	125	0.565	76.2	+15	11 V., 9 S.	18.8	10.2	12.6	3.8	214

* One of group of 100 "normal" men.

TABLE 25.—*The Results of Examinations of the Twenty Persons with the Highest Basal Metabolic Rates*

Individual Number	Basal Metabolic Rate	Diagnosis	Blister Time, Hr.	Permeability Ratio	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Skin Resistance	Pulse Rate	Epinephrine, Pulse Pressure, % Increase	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Weight/Length Ratio	Kromayer Light Erythema Time, Min.
126	+105	Exophthalmic goiter	6	..	9.8	18	1.83	0.20	90	+20	Sympatheticotonic	19.6	7	12	0	174	...
131	+ 88	Exophthalmic goiter	5	77	10.6	18	1.7	0.21	...	....	.....	16.8	6.2	10.4	6.2	177	135
31	+ 73	Exophthalmic goiter	5.5	70	9.5	....	....	....	114	....	.....	21.6	7	7.2	0	200	...
51	+ 67	Exophthalmic goiter	5.5	77	10	25.8	2.58	0.13	104	+25	Sympatheticotonic	19.2	6.2	9.2	4.8	195	...
125	+ 59	Exophthalmic goiter	6	74	11.51	....	....	0.48	140	....	.....	20.4	7	15.2	16.4	197	90
88*	+ 54.6	Tuberculosis	7.25	58	9.4	13.1	1.4	0.68	76	—10	Vagotonic	18.4	11	12.4	12	203	120
9	+ 49	Exophthalmic goiter	5.5	71	11.5	23.5	2.04	0.75	96	+28	Sympatheticotonic	....	....	....	....	200	120
110*	+ 48.8	Healed tuberculosis	7.5	54	12.1	16.3	1.34	0.60	84	— 4	Vagotonic	20.8	4.2	12	9.4	190	240
123	+ 48	Carcinoma of thyroid	9.25	74	9.2	20	2.7	....	80	— 3	Sympatheticotonic	20	6.8	10	12.2	263	...
159	+ 46	Exophthalmic goiter	5	69	8.23	17.9	2.17	0.22	76	+17	.....	25	9	12	0	181	70
22	+ 44	Exophthalmic goiter	6	73	12.1	18.2	1.5	0.17	92	+31	Sympatheticotonic	26.4	10	5	1	233	75
58	+ 43.1	Exophthalmic goiter	5	75	12	25.9	2.15	0.10	127	+ 2	Sympatheticotonic	19.6	10.4	11.2	6.8	188	66
11	+ 42	Exophthalmic goiter	5	70	10.9	24.1	2.21	0.14	108	+06	Sympatheticotonic	....	....	....	....	195	180
150	+ 39	Glaucoma	15	58	12	21.3	1.78	0.22	84	+ 6	Sympatheticotonic	17	14	16	0	238	95
158	+ 37	Hodgkin's disease	15	61	9.33	18.53	2	0.29	96	+10	Sympatheticotonic	19.2	11.3	28	0	173	60
81*	+ 34.8	Cardiovascular renal condition	6	59	8.4	25.8	3.07	0.10	76	+ 4	Vagotonic	14	6.2	10	0	209	90
47*	+ 34	Healed tuberculosis	5	62	10.4	26.2	2.51	0.13	70	— 5	Vagotonic	21.6	5.2	9	0	260	90
119	+ 34	Adenoma of thyroid	6.45	58	9	18.7	2.1	0.08	96	+13	Sympatheticotonic	24	5	12	7	266	75
170	+ 33	Glaucoma	15	72	10.58	23.71	2.2	0.07	104	....	.....	....	....	....	....	170	...
67*	+ 32	Dwarf	6	71	8.8	17.6	2	0.19	75	+ 8	Vagotonic	17.2	9	13.6	0	195	80
	50.5	Averages and totals	7.3	67.5	9.81	20.7	2.07	0.26	94.1	+ 8	10 S., 5 V.	20	7.9	12	4.9	205	105.7

* One of group of 100 "normal" men.

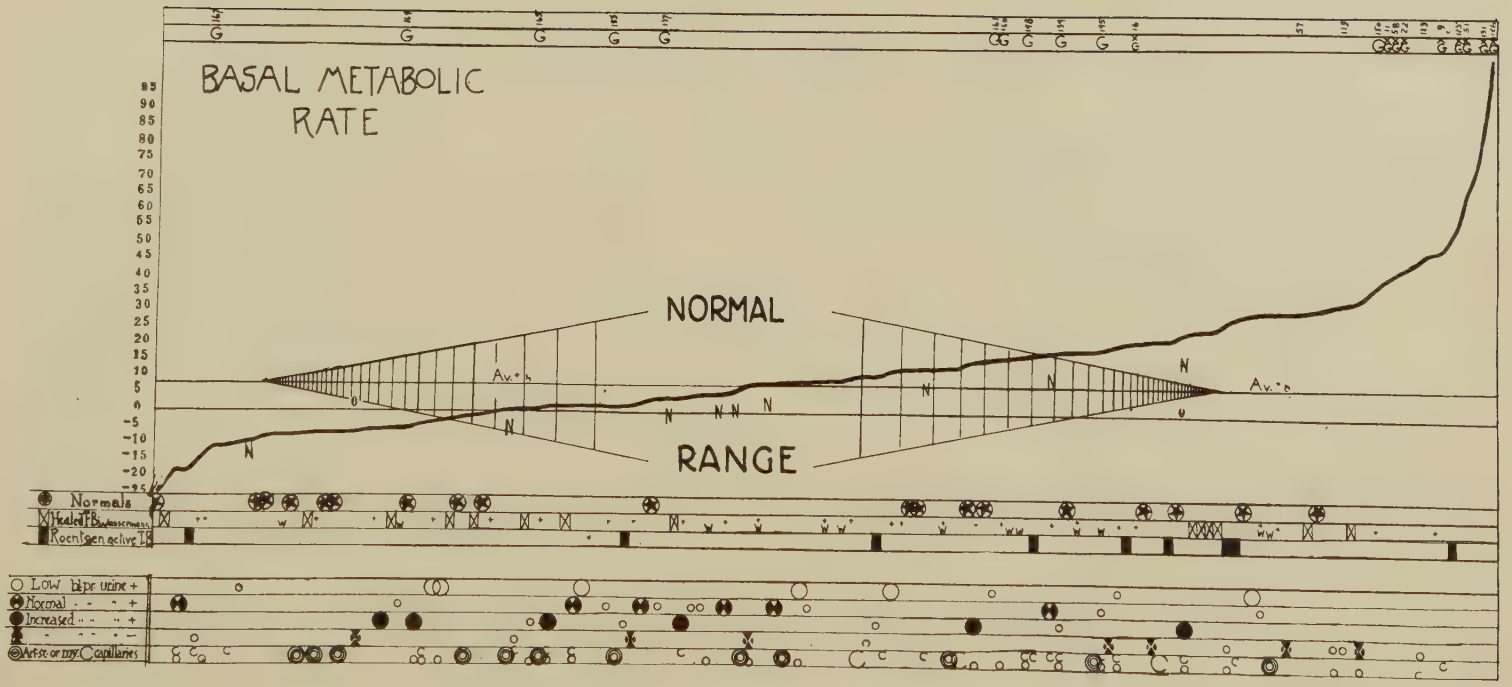

Chart 8.—The basal metabolic rate of normal persons and patients with various clinical conditions.

and the probability exists that, in some cases, food or stimulants had been taken in the morning before the examination.

We have prepared two tables, one including those persons with low basal rates (table 24) and a second including those with extremely high rates (table 25). In this latter table, we have retained the results of the examinations of persons with exophthalmic goiter, contrary to the practice followed in the other tables of results. It will be noted that those with low rates have longer blister times, higher levels of calcium and lower K/Ca ratios, longer Kromayer reaction times and greater skin resistance. They have slower pulse rates and are slightly heavier. The subcutaneous injection of epinephrine hydrochloride shows that, as far as the effect on pulse pressure is concerned, the group with the low ratios has an increase of +15 per cent as compared with +8 per cent of the group with the high ratios, but that there are more sympatheticotonic types in the latter group. The intracutaneous injections indicate that the group with the high ratios has smaller flares due to epinephrine and larger flares due to thyroxin.

Examination of chart 8 indicates that the group with roentgenologic evidence of active tuberculosis has higher rates. There is no apparent connection with the cardiovascular renal condition.

RESISTANCE OF THE SKIN TO ELECTRIC CURRENT

The resistance of the skin to electric current varies from a "low" of 0.07 megohms to a "high" of 6.1. The average for the entire group of 100 "normal" men is 0.46.

For the actually normal persons, the range is approximately from 0.15 to 0.45 (average 0.33). Two of our normal group fall outside these limits, patients 29 and 78. These persons have repeatedly been found at the extremes or beyond the normal range, patient 29 being the one in whom a trace of bile was found in the urine.

In table 26, the results of examinations of the ten persons with the lowest skin resistance are tabulated, and in table 27, those of the ten persons with the highest resistance.

Chart 9 shows the curve of the skin resistance. It will be noted that the majority of the persons with roentgenologic evidence of active tuberculosis are on the side of low resistance. There appears to be nothing characteristic about the persons with cardiovascular renal conditions; the persons with glaucoma are scattered over the entire range. On the other hand, the persons with exophthalmic goiter appear to be on the side of low resistance.

TABLE 26.—*The Results of Examinations of the Ten Persons with the Lowest Resistance of the Skin to Electric Current*

Individual Number	Skin Resistance	Diagnosis	Permeability of Capillaries	Basal Metabolic Rate	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
138	0.07	Fröhlich's syndrome	73	+ 8	270	Vagotonic	23	9.5	17	6.5
170	0.07	Glaucoma	72	+33	170	.....	....	....	....	...
172	0.08	Syphilis; Raynaud's disease	72	+18	166	Sympathetic-cotonic	22.4	16	18	16
166	0.08	Eosinophilia	57	— 7	200	Vagotonic	17	11.5	18	0
28	0.08	Healed tuberculosis	64	+24.5	200	Sympathetic-cotonic	20	12.2	7.4	0
104	0.08	Tuberculosis	54	+27.5	235	Vagotonic	20.8	6.2	12	0
154	0.09	Glaucoma; arteriosclerosis	60	+18	181	.....	23	10	26	0
173	0.09	Tumor of the cord	57	+12	177	Sympathetic-cotonic	21	12.5	18	0
105	0.09	Healed tuberculosis	62	+31.6	194	Vagotonic	19.6	5.6	12	10.4
135	0.09	Nervous	84	+17	183	Vagotonic	12.4	3.2	20	0
	0.07	Averages	65.5	18.26	197		20	9.5	16.5	

TABLE 27.—*The Results of Examinations of the Ten Persons with the Highest Resistance of the Skin to Electric Current*

Individual Number	Skin Resistance	Diagnosis	Permeability of Capillaries	Basal Metabolic Rate	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
27	6.1	Lead poisoning; syphilis	82	+17	217	.....	....	....	....	....
112	2.7	Arteriosclerosis; cardiovascular renal condition	54	+19.6	218	Vagotonic	22.4	7.2	9.8	0
73	2.0	Syphilis	69	+16.3	191	Vagotonic	17.6	8.2	15.6	0
118	1.9	Tuberculosis; arthritis	87	—11	154	Vagotonic	16.8	7.4	12	8.6
137	1.9	Glaucoma	61	+ 3.6	16.6	Vagotonic	15.4	10.5	13	0
69	1.9	Nervous; ulcer	51	+ 4	160	Sympathetic-cotonic	21	10	14.4	10.2
33	1.8	Epilepsy	73	—18	240	Sympathetic-cotonic	20	12.6	5.4	0
46	1.7	Inanition	59	+13	168	Sympathetic-cotonic	21.2	13.2	12.2	11.2
80	1.6	Nervous	91	+13	212	Vagotonic	14.8	12.4	13.4	9.2
161	1.4	Nervous; glaucoma	72	—16	171	Sympathetic-cotonic	14	13	13	0
	2.3	Averages	69.9	7.4	189.7		18	10.5	12	

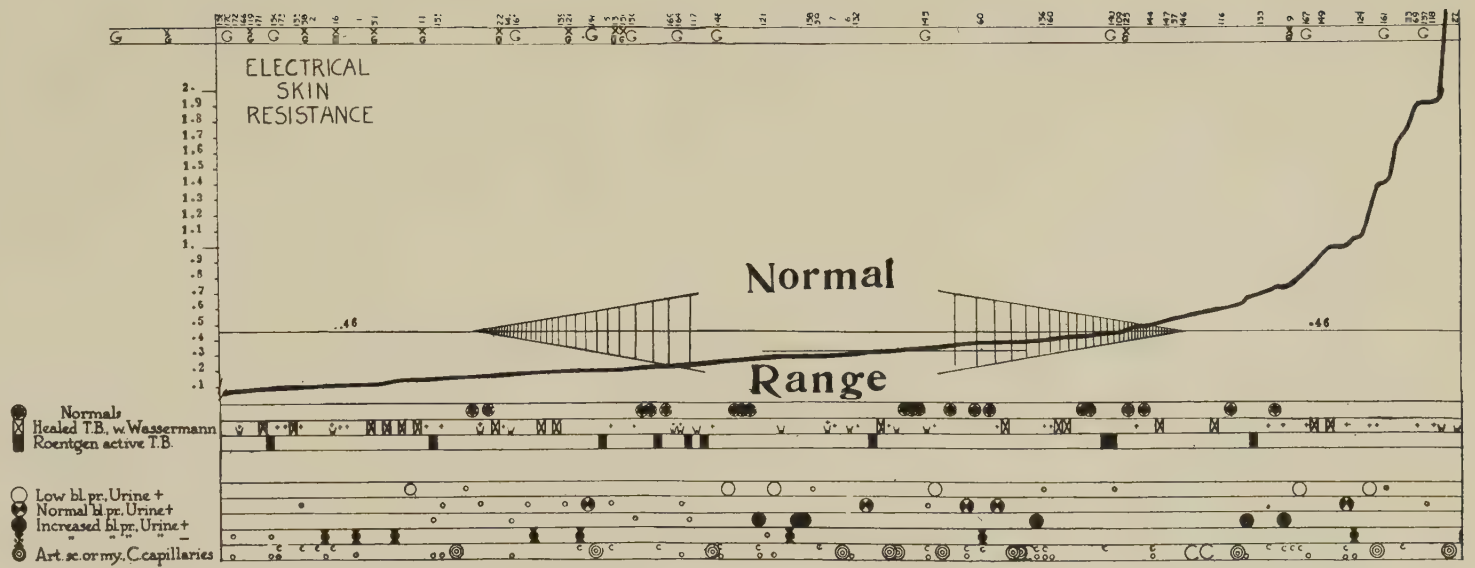

Chart 9.—The resistance of the skin to electric current of normal persons and patients with various clinical conditions.

MUSCLE REACTIVITY

Hopman [10] has sought to establish the fact that the muscle irritability may be used as a criterion of the autonomic status of a person at the time of examination. In general, it has been assumed that the vagotonic person inclines toward alkalosis and, therefore, shows a greater irrita-

TABLE 28.—*The Results of Examinations of the Twenty Persons with the Highest Reactivity of the Muscles*

Individual Number	Muscle Reaction	Diagnosis	CO_2 Combining Power	Potassium, Mg.	K / Ca Ratio	Skin Resistance to Electric Current	Weight/Length Ratio	Pulse Rate	Vascular Reaction to Epinephrine	Systolic Blood Pressure
140	0.2	Glaucoma; tuberculosis; sensitized	55.6	29.7	2.61	0.45	...	70	Vagotonic	100
132	0.3	Sensitized; healed tuberculosis; eczema	40.3	15	1.12	0.31	234	56	Vagotonic	132
65*	0.4	Cardiovascular renal condition	53.1	16.4	1.67	0.80	221	63	Sympathetic-cotonic	100
141	0.4	Glaucoma	64.6	28.2	....	0.20	...	84	Vagotonic	118
108*	0.6	Tuberculosis	54.1	15.3	1.47	0.44	196	71	Sympathetic-cotonic	94
55*	0.6	Cardiovascular renal condition	56.6	24.9	3.10	0.38	170	84	Vagotonic	128
128*	0.6	Sensitized; cardiovascular renal condition	58.1	19.7	1.93	1	180	84	Sympathetic-cotonic	122
139	0.8	Urticaria	50	18.4	1.90	0.20	176	104	Vagotonic	113
137	0.8	Glaucoma	51.9	18.2	2.24	1.90	166	78	Vagotonic	119
52*	1	Healed tuberculosis	52.9	20.9	2	0.13	213	75	Vagotonic	110
78*	1	Normal	62.7	18.8	2.23	0.62	203	74	Sympathetic-cotonic	122
135	1	Nervous	54.5	19.6	1.65	0.09	183	88	Vagotonic	120
77*	1	Sensitized	60.6	15.6	1.44	1	187	82	Vagotonic	126
56*	1	Tuberculosis	56.6	28.6	2.52	0.32	247	80	Vagotonic	124
117	1	Syphilitic arthritis	52.4	17.5	1.80	0.25	195	78	Sympathetic-cotonic	130
29*	1	Normal (bile in urine)	60.1	23.9	2.39	0.74	214	76	Sympathetic-cotonic	134
7	1.2		55	....	....	0.30	202	68	.....	118
25*	1.2	Tuberculosis	59.8	28.8	2.60	0.24	183	86	Sympathetic-cotonic	140
14*	1.2	Syphilis; cardiovascular renal condition	55.3	18.3	1.55	0.33	200	92	Sympathetic-cotonic	122
104*	1.2	Tuberculosis	57.2	22.9	3.09	0.08	235	84	Vagotonic	176
	0.82	Averages and totals	55.5	21	2.07	4.89	200	78.8	11 V., 8 S.	122

* One of group of 100 "normal" men.

bility. We have not been able to find any such correlation. Goebel and Hillenberg [11] were unable to confirm Hopman's conclusions. In the acidosis of pregnancy, Adersberg and Klafter [12] found a distinct increase in irritability.

10. Hopman, R.: Klin. Wchnschr. **5**:1553, 1926.
11. Goebel, F., and Hillenberg, S.: Arch. f. Kinderh. **78**:1, 1926.
12. Adersberg, D., and Klafter, E.: Klin. Wchnschr. **6**:2091, 1927.

When the tables of the results of the examinations of our extreme cases are examined, we find a distinct difference in the types of cases comprising them, as well as marked differences in the blood chemistry. Thus, it will be found that in the group with the greatest irritability are included a number of persons with roentgenologic evidence of active

TABLE 29.—*The Results of Examinations of the Twenty Persons with the Lowest Reactivity of the Muscles*

Individual Number	Muscle Reaction	Diagnosis	CO_2 Combining Power	Potassium, Mg.	K / Ca Ratio	Skin Resistance to Electric Current	Weight/Length Ratio	Pulse Rate	Vascular Reaction to Epinephrine	Systolic Blood Pressure
94*	10	Normal	55.1	17.5	2.08	0.45	236	53	Vagotonic	134
76*	9.6	Cardiovascular renal condition	57.9	20.2	1.87	0.28	230	64	Sympathetic-cotonic	108
71*	9	Cardiovascular renal condition	57.9	17.5	2	0.36	195	88	Vagotonic	114
39*	8.5	Syphilis	55.7	18	1.91	0.29	254	82	Vagotonic	138
79*	7.7	Ulcer; cardiovascular renal condition	57	20	1.78	0.71	220	76	Sympathetic-cotonic	140
61*	7.4	Cardiovascular renal condition	53.1	17.9	2.35	0.28	208	64	Vagotonic	142
45*	7.4	Cardiovascular renal condition	54.3	16.6	1.48	0.28	317	84	Vagotonic	162
32*	7.4	Cardiovascular renal condition	54.1	26.1	2.73	0.18	190	74	Vagotonic	144
53*	6.7	Normal	53.9	22.8	....	0.35	231	80	Vagotonic	125
15*	6	Healed tuberculosis	57.6	18.8	1.55	0.19	210	60	Sympathetic-cotonic	128
17*	6	Normal	59.1	18.2	1.43	0.22	216	66	Vagotonic	130
82*	5.7	Cardiovascular renal condition	58.8	17.2	1.50	0.20	208	62	Sympathetic-cotonic	170
98*	5.5	Cardiovascular renal condition	62.7	17	1.93	0.20	212	64	Vagotonic	136
75*	5.4	Cardiovascular renal condition	61.6	19.2	1.78	0.13	243	77	Vagotonic	146
47*	5	Healed tuberculosis	56.4	26.2	2.51	0.13	260	70	Vagotonic	136
20*	5	Tuberculosis	62.7	17.4	1.53	0.25	226	80	Vagotonic	130
62*	5	Cardiovascular renal condition	56.8	15.2	1.30	0.15	221	64	Vagotonic	140
64*	5	Normal; nervous	55	16.6	1.84	0.22	208	64	Vagotonic	112
68*	4.4	Healed tuberculosis	51.1	17.1	1.94	0.53	217	89	Sympathetic-cotonic	131
63*	5	Cardiovascular renal condition	62.4	20.9	1.83	0.65	190	60	Vagotonic	116
	6.58	Averages and totals	57.1	19.1	1.85	0.30	224	71	15 V., 5 S,	134

* One of group of 100 "normal" men.

tuberculosis, as well as sensitized persons. In the group with the lower irritability are many persons with cardiovascular renal lesions and increased blood pressure (tables 28 and 29).

The persons with the greatest irritability have more serum potassium, higher K/Ca ratios, greater skin resistance and higher pulse rates and are somewhat lighter in weight.

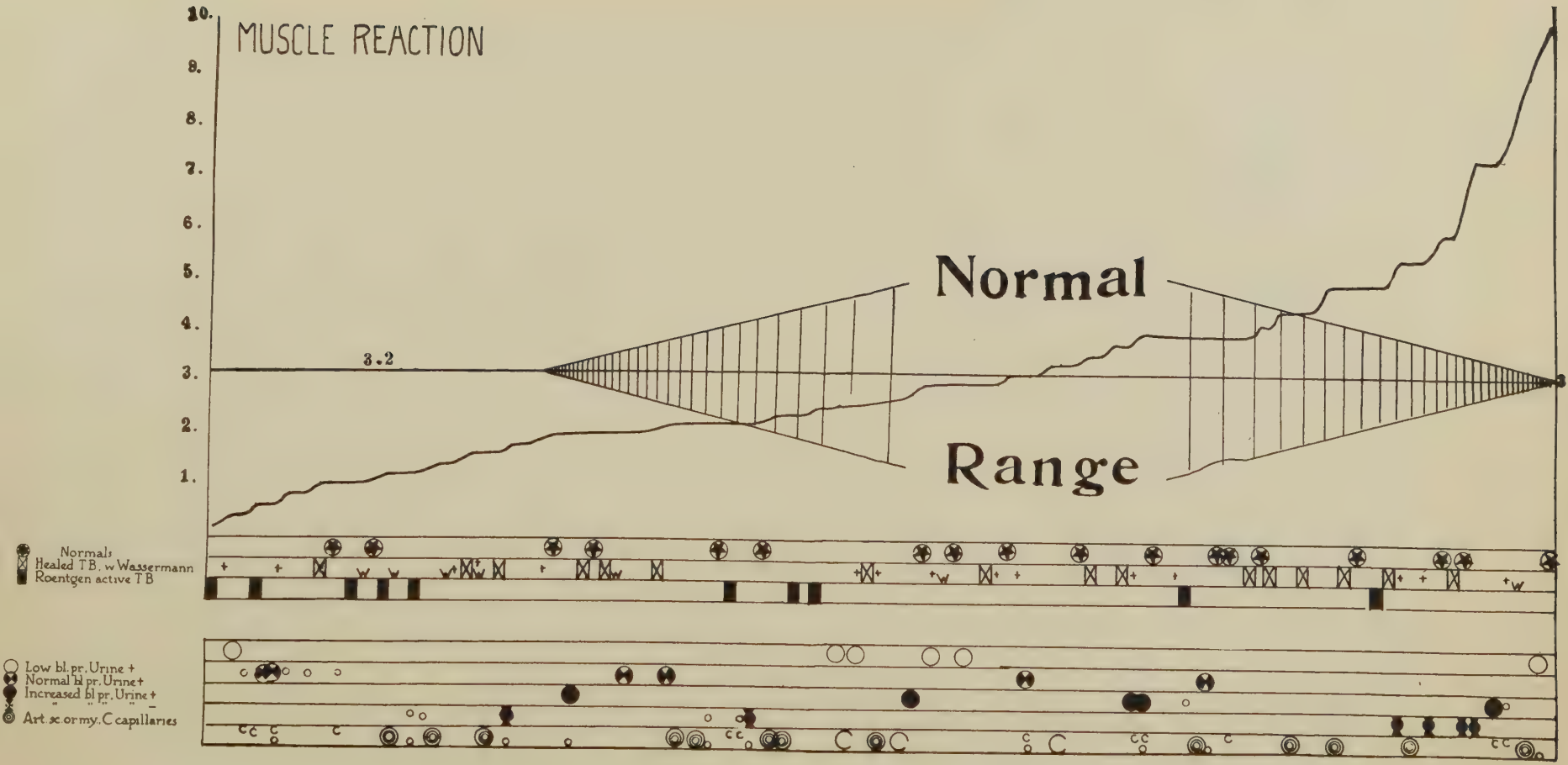

Chart 10.—The muscle reactivity of normal persons and patients with various clinical conditions.

REACTION OF PULSE PRESSURE TO EPINEPHRINE

On page 121, we report an analysis of the present material when the results of the reaction to epinephrine (subcutaneous injection of 0.5 cc. of epinephrine hydrochloride, 1 to 1,000) are estimated wholly on the increase or decrease in the systolic blood pressure. There, we point out that when we select a group of ten of the most markedly sympatheticotonic persons and compare them with the ten most markedly vagotonic persons, the sympatheticotonic ones have higher calcium levels, but lower K/Ca ratios, shorter Kromayer lamp erythema times, lower blood pressures and CO_2 combining powers, lower weight/length ratios and somewhat greater wheals due to thyroxin, and greater flares due to epinephrine and thyroxin.

When we examine tables 30 and 31 containing the results of the examinations of the twenty persons showing the greatest and the least reactivity to epinephrine based on the percentage of increase or decrease in pulse pressure for one hour following the injection, we, of course, deal with a somewhat different group of persons. In both instances, we deal with persons who give either a primary sympatheticotonic or a vagotonic systolic reaction, but inclusion in this group will depend rather on the sustained character of these reactions.

The blister times for the sympatheticotonic group so constituted are longer, the levels of calcium are somewhat higher, the blood pressures are lower, the levels of the blood sugar are higher and the persons are not so heavy. The flares due to epinephrine and the wheals due to thyroxin are larger.

In our former study of this material, we found that the low K/Ca ratio which Kylin assumed for the sympatheticotonic group was apparent only for a relatively small, selected group, while many of the persons with a distinctly sympatheticotonic type of reaction had high ratios. It should be noted that with the present classification, the difference in the ratio which Kylin postulates does not appear. In general, however, the sympatheticotonic group has a higher level of calcium.

Chart 11 reveals the wide range of our normal persons, as well as of the persons with cardiovascular renal conditions. In the latter group, however, certain differences do appear. Those with low blood pressures and positive evidence of changes in the urine appear at the vagotonic end. Patients with exophthalmic goiter, as might be anticipated, are found toward the sympatheticotonic end.

TABLE 30.—*The Results of Examinations of the Twenty Persons with the Greatest Increases of Pulse Pressure Following the Subcutaneous Injection of Epinephrine Hydrochloride*

Individual Number	Reaction to Epinephrine: Pulse Pressure Increase, %	Diagnosis	Blister Time, Hr.	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Globulin, Mg.	Blood Pressure, Systolic	Blood Pressure, Diastolic	Sugar, Mg.	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
8*	90	Normal	10	64	6.4	10.5	21	2	45	120	86	73	197	Sympatheticotonic +	20.4	9.8	14.2	0
54*	66	Cirrhosis; cardiovascular renal condition	6	60	10	....	22	....	33	108	68	80	256	Sympatheticotonic —	21.2	13.4	12	0
2*	64	Epilepsy	7	69	9.8	12.9	26.1	2	..	100	68	74	...	Sympatheticotonic +	....	....	....	....
167	62	Glaucoma	15	56	3.7	12	22.7	1.9	27	137	92	81	158	Sympatheticotonic +	17	14.2	15	0
127*	60	Cardiovascular renal condition	13	50	3.8	12.2	16.2	1.33	33	106	76	81	180	Sympatheticotonic +	18.4	9.7	15.4	12
172	57	Raynaud's disease	12	72	6	13	21.3	1.64	..	108	78	76	166	Sympatheticotonic +	22.4	16	18	16
24*	50	Healed tuberculosis	6	70	11.6	11.7	24.8	2.12	60	116	58	81	219	Sympatheticotonic +	16.8	12.6	6.6	0
144	50	Cardiovascular renal condition; pellagra	15	35	2.2	9.8	17.9	1.79	2	100	80	90	174	Sympatheticotonic +	14.4	11.5	15	0
92*	46	Nervous	9	82	9	8.4	19.5	2.32	26	110	60	67	210	Sympatheticotonic +	20.4	10.2	15.2	7.6
145	43	Glaucoma	15	67	4.4	10.1	15.7	1.55	55	136	80	70	166	Sympatheticotonic —	18	13.6	16	0
87*	40	Normal	6	56	9.3	8.4	19.5	2.32	30	104	62	94	200	Sympatheticotonic +	16	8.8	12	5.4
66*	37	Cardiovascular renal condition	6	78	13	11	20	1.8	..	128	66	67	257	Sympatheticotonic +	20	9.2	10.2	0
133	36	Scleroderma	..	..	....	13.2	17.5	1.32	90	92	68	77	...	Sympatheticotonic +	....	....	....	....
1	35	Neurosis	8	68	8.5	12.1	24.9	2	38	132	74	113	202	Sympatheticotonic +	20	8	13.2	9.6
25*	35	Tuberculosis	6	57	9.5	11.1	28.8	2.6	19	140	80	67	183	Sympatheticotonic	21.2	12.2	9	15.2
142	33	Tumor of the brain	7	54	7.7	9.4	18.3	1.95	19	108	78	97	200	Sympatheticotonic	18.6	8.7	17	0
35*	33	Normal	8	54	6.7	8.7	25.2	2.9	33	108	78	79	203	Sympatheticotonic —	22.8	11	9.2	0
53*	32	Normal	8	62	7.7	....	22.8	....	25	125	73	77	231	Sympatheticotonic —	17.2	11.8	12.2	11.2
68*	31	Healed tuberculosis	7	78	11	8.8	17.1	1.94	30	131	76	68	217	Sympatheticotonic	19.2	9.6	12	7
82*	31	Cardiovascular renal condition	6	58	9.6	11.4	17.2	1.5	33	170	98	58	208	Sympatheticotonic +	21.2	7	11	0
20	41	Averages	8.9	62	7.8	10.8	20.9	1.93	35	113	73	78	195		20	10.8	13	4.6

* One of group of 100 "normal" men.

TABLE 31.—*The Results of Examinations of the Twenty Persons with the Lowest Increases of Pulse Pressure Following the Subcutaneous Injection of Epinephrine Hydrochloride*

Individual Number	Reaction to Epinephrine: Pulse Pressure Increase, %	Diagnosis	Blister Time, Hr.	Permeability of Capillaries	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Globulin, Mg.	Blood Pressure, Systolic	Blood Pressure, Diastolic	Sugar, Mg.	Weight/Length Ratio	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
116	—17	Urticaria	3.5	60	17	10	19.4	1.94	40	128	50	78	195	Vagotonic	20.4	7.4	5	0
121	—13	Arthritis deformans	6	69	11.5	8.9	20.2	2.27	30	148	80	74	294	Vagotonic	26	5.6	8	0
86*	—12	Nervous	15	58	3.8	12.6	15.9	1.26	40	118	60	94	176	Vagotonic	18.8	14	15.4	12.4
129*	—10	Tuberculosis	15	52	3.5	11.5	19	1.65	42	116	66	83	219	Vagotonic	18.4	7	12.2	0
88*	—10	Tuberculosis	7.25	58	8.1	9.4	13.1	1.4	33	128	76	79	203	Vagotonic	18.4	11	12.4	12
135	—10	Nervous	6	84	14	11.9	19.6	1.65	45	120	60	75	183	Vagotonic	12.4	3.2	20	0
75*	— 9	Cardiovascular renal condition	9	60	6.6	10.8	19.2	1.78	38	146	80	75	213	Vagotonic	20.4	10.8	10	0
118	— 8	Arthritis	10	87	8.7	12.2	17.2	1.4	38	120	60	80	154	Vagotonic	16.8	7.4	12	8.6
67*	— 8	Dwarf	6	71	11.8	8.8	17.6	2	33	128	80	56	195	Vagotonic	17.2	9	13.6	0
37*	— 8	Normal	9	56	6.2	10	22.6	2.26	42	116	70	75	254	Vagotonic	20.4	21.6	10	0
70*	— 8	Arthritis	10.5	74	7	11.4	16.6	1.45	34	148	50	67	234	Vagotonic	18	11	10	0
47*	— 5	Healed tuberculosis	5	62	12.8	10.4	26.2	2.51	40	136	64	72	260	Vagotonic	21.6	5	9	0
152	— 5	Angioneurotic edema	4	73	18	9.8	20.1	2.05	20	120	74	63	243	Vagotonic	26	7.5	9	8
106*	— 5	Cardiovascular renal condition	6	71	12	11.2	19	1.69	37	120	80	65	243	Vagotonic	19.6	7	11.2	0
110*	— 4	Healed tuberculosis	7.5	54	7.2	12.1	16.3	1.34	28	110	62	61	190	Vagotonic	20.8	4.2	12	9.4
123	— 3	Carcinoma of thyroid; hyperthyroidism	9.25	74	8	9.2	20	2.17	32	165	110	81	263	Vagotonic	20	6.8	10	12.2
45*	— 3	Cardiovascular renal condition	6	54	9	11.2	16.6	1.48	40	162	114	77	317	Vagotonic —	20.4	9.8	16.4	12
122*	— 3	Normal	4	68	17	10.6	19.2	1.81	35	102	50	50	189	Vagotonic —	20	7.8	12	9
103*	— 1	Cardiovascular renal condition	6	52	8.6	9.2	17.3	1.88	40	126	70	57	270	Vagotonic —	22.4	9	12.2	0
107*	— 1	Cardiovascular renal condition	9	58	6.4	8	18.4	2.3	40	134	72	60	265	Vagotonic	20.8	5.8	13.4	6.2
	— 7	Averages	7.7	64	9.6	10.4	18.6	1.8	44	128	71	71	232		19.8	8.3	11.6	4.4

* One of group of 100 "normal" men.

Chart 11.—The pulse pressure increase following the subcutaneous injection of epinephrine hydrochloride in normal persons and patients with various clinical conditions.

CO_2 COMBINING POWER

The average CO_2 combining power of the serum of the 100 "normal" men was 57.7. The range for the strictly normal persons was from 52 to 65. Chart 12 indicates that all the persons in the healed tuberculous group are uniformly distributed over the normal range; the per-

TABLE 32.—*The Results of Examinations of the Ten Persons with the Lowest CO_2 Combining Powers*

Individual Number	CO_2 Combining Power	Diagnosis	Potassium, Mg.	Calcium, Mg.	Ice Reaction Time, Seconds	Weight/Length Ratio	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
132	40.3	Eczema	15	13.4	10	234	18.4	9.4	13.4	5
167	47.9	Glaucoma	22.7	12	5	158	17	14.2	15	0
171	48.7	Urticaria	17.9	12.6	20	161	17.5	10.5	18	0
161	49.4	Glaucoma	18	9.2	12	171	14	13	13	0
106	49.5	Cardiovascular renal condition	19	11.2	30	243	19.6	7	11.2	0
139	50	Urticaria	18.4	9.7	8	176	16	11	14	12.5
68	51	Healed tuberculosis	17.1	8.8	10	217	19.2	9.6	12	7
109	51.4	Neurosis	16.1	10.8	25	140	18	9	12	9.4
115	51.8	Cardiovascular renal condition	15.2	7.8	10	215	17.2	6	14.2	8
137	51.9	Glaucoma	18.2	8.1	30	166	15.4	10.5	13	0
	49.2	Averages	17.7	10.36	16	188	17.2	10	13.5	4.19

TABLE 33.—*The Results of Examinations of the Ten Persons with the Highest CO_2 Combining Powers*

Individual Number	CO_2 Combining Power	Diagnosis	Potassium, Mg.	Calcium, Mg.	Ice Reaction Time, Seconds	Weight/Length Ratio	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
153	73.2	Glaucoma	18.7	9	30	223	22	6.5	18	0
150	72.7	Glaucoma	21.3	12	7	238	17	14	16	0
146	71	Myasthenia	14.4	9.2	30	192	18	12	19	0
148	69.6	Glaucoma	24.3	9.7	10	182	18	12	17	0
28	66	Healed tuberculosis	24.1	11	25	200	20	12.2	7.4	0
149	65.4	Nervous	17	10.1	15	209	20	9.7	19	0
14	65	Cardiovascular renal condition	19.6	11.2	40	198	24.4	6.2	15	5
50	65	Normal	27.4	18.4	15	237	24.8	10.6	10.4	10
4	64.3	Normal	21.2	11.8	40	237	22.8	10.6	10.2	0
105	64.4	Healed tuberculosis	17.1	9	15	194	19.6	5.6	12	10.4
	67.6	Averages	20.5	10.4	22.7	211	20.6	9.94	14.4	2.5

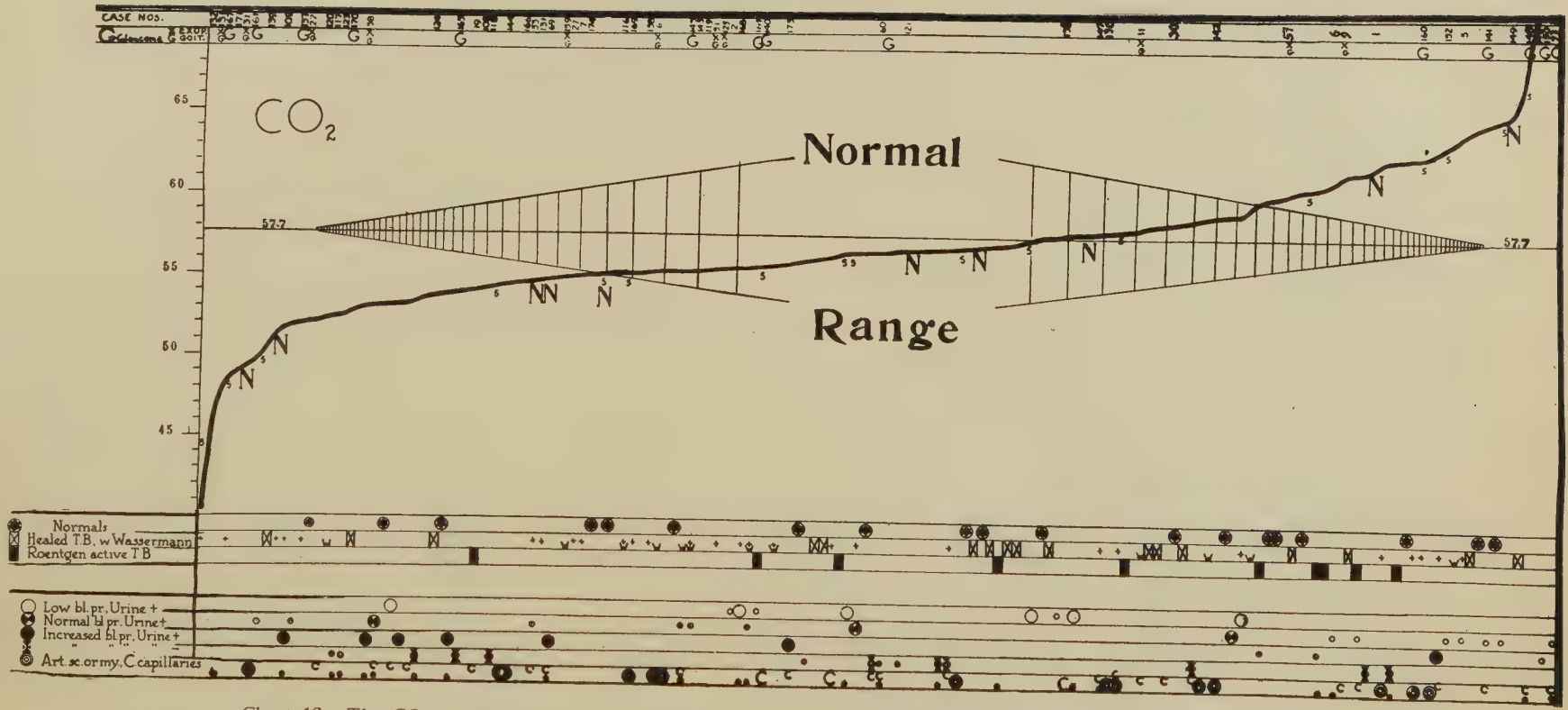

Chart 12.—The CO_2 combining power of the serum of normal persons and patients with various clinical conditions.

sons with active tuberculosis tend to appear at the upper end of the curve. There appears to be nothing characteristic in the distribution of the various groups with cardiovascular renal conditions, unless it is the fact that those with increased blood pressure and urinary changes appear at the low end of the scale.

Sensitized and nervous persons are found over the entire range. More of the patients with exophthalmic goiter and glaucoma are found on the side below the average.

We have tabulated the results of some examinations of the ten persons with the lowest and of the ten with the highest CO_2 combining powers in tables 32 and 33.

It will be observed that the person (no. 132) with the lowest CO_2 combining power is the one with eczema who previously was outstanding because of a low K/Ca ratio. Two persons with urticaria also appear in this group. The types of persons in the group with high CO_2 combining power are of no particular interest. The chief divergencies of the group with low CO_2 combining power appear to be their shorter ice reaction times and smaller wheals due to epinephrine. The potassium values, too, are perceptibly diminished.

ICE REACTION TIME

The rapidity with which an erythema appears following the local application of ice to the skin affords some insight concerning the activity of the peripheral vasomotor apparatus. In these observations, we have uniformly used the chest wall. In the table of correlation (part I, table 1), we have shown the following apparent correlations of the ice reaction time: delay of the reaction (1) with increasing level of calcium; (2) with increasing metabolic rate; (3) with increasing CO_2 combining power (except with exophthalmic goiter); (4) with increasing age; (5) with decrease of the flare due to thyroxin and of the wheal to caffein; and acceleration with increasing weight/length ratio.

Tables 34 and 35, based, respectively, on the extremely rapid reaction and the delayed reaction, confirm the relation to the level of calcium, to the metabolic rate, to the weight/length ratio, to age and to the flare due to thyroxin. In addition, it appears that with delayed ice reaction, the resistance of the skin to electric current is greater. The proportion of sympatheticotonic persons is slightly larger in the group with short ice reaction time.

When we examine chart 13, we find the strictly normal group scattered over the entire curve, but it may be observed that almost half of the group are clustered in one region (the range from 18 to

TABLE 34.—*The Results of Examinations of the Twenty Persons with the Most Rapid Reactions to Local Application of Ice to the Chest*

Individual Number	Ice Reaction Time, Seconds	Diagnosis	Calcium, Mg.	Inflammatory Index	Protein, Mg.	Skin Resistance to Electric Current	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Thyroxin, Flare, Mm.	Caffein, Wheal, Mm.	Weight/Length Ratio	Age
67*	4	Dwarf	8.8	11.8	6.98	0.19	32	Vagotonic	0	33.4	195	47
122*	5	Normal	10.6	17	8.06	0.37	—7.3	Vagotonic	9	21.2	189	33
100*	5	Healed tuberculosis	9	9	7.85	0.11	—1.6	Vagotonic	29.2	27	241	45
165	5	Glaucoma	10	5.4	8.28	0.18	0.5	.....	0	15	250	52
168	5	Orthostatic albuminuria	9.4	12	7.41	0.16	—9	Vagotonic	0	22	215	28
167	5	Glaucoma	12	3.7	8.71	0.85	—13	Sympathetic-otonic	0	....	158	77
142	5	Tumor of the brain	9.4	7.7	7.69	0.17	+5	Sympathetic-otonic	0	30	200	53
103*	5	Cardiovascular renal condition	9.2	8.6	7.73	0.39	+2	Vagotonic	0	18.2	270	59
61*	7	Cardiovascular renal condition	7.6	11.6	7.41	0.28	+1	Vagotonic	0	20.2	208	51
41*	7	Normal	9.8	9.1	8.49	0.26	+15	Vagotonic	0	5.8	216	40
10*	7	Healed tuberculosis	10.1	13	8.70	0.42	—12.4	Vagotonic	7.2	12.2	230	40
64*	7	Normal	9	10	7.41	0.22	+23	Sympathetic-otonic	11.6	16.2	208	31
43*	7	Normal	9.2	9.7	7.63	0.27	—4.4	Sympathetic-otonic	0	11	231	45
150	7	Glaucoma	12	3.8	7.85	0.22	+39	Vagotonic	0	22	238	67
139	8	Urticaria	9.7	11	7.10	0.20	+5	Vagotonic	12.5	14	176	29
78*	10	Normal	8.4	12	8.49	0.62	—6.2	Sympathetic-otonic	6.2	20	203	33
18*	10	Healed tuberculosis	14.5	8.7	8.30	1	+4.2	Vagotonic	....	....	200	31
95*	10	Healed tuberculosis	7.8	9.8	8.5	0.39	+26	Sympathetic-otonic	6.2	26.2	220	54
59*	10	Normal	9.6	8.6	7.85	0.16	—6.5	Vagotonic	8	23.4	252	37
68*	10	Healed tuberculosis	8.8	11	8.66	0.53	+25.8	Sympathetic-otonic	7	22.4	217	35
	6.9	Averages and totals	9.74	9.67	7.95	0.349	+5.9	7 S., 12 V.	5.1	20	215	44.3

* One of group of 100 "normal" men.

TABLE 35.—*The Results of Examinations of the Twenty Persons with the Least Rapid Reactions to the Application of Ice to the Chest*

Individual Number	Ice Reaction Time, Seconds	Diagnosis	Calcium, Mg.	Inflammatory Index	Protein, Mg.	Skin Resistance to Electric Current	Basal Metabolic Rate	Vascular Reaction to Epinephrine	Thyroxin, Flare, Mm.	Caffein, Wheal, Mm.	Weight/Length Ratio	Age
91*	45	Cardiovascular renal condition	....	8	7.85	0.30	— 1.7	Vagotonic	9.4	22.2	208	66
70*	45	Arthritis; cardiovascular renal condition	11.4	7	8.65	0.39	+23	Vagotonic	0	24.6	264	65
81*	45	Pruritis; cardiovascular renal condition	8.4	10	8.49	0.10	+34.8	Vagotonic	0	16.4	209	69
136	45	Arteriosclerosis; pellagra	10	5	9.28	0.39	+20	Sympathetic-otonic	0	16	180	44
172	45	Raynaud's disease	13	6	8.16	0.08	+18	Sympathetic-otonic	16	20	166	30
14*	40	Cardiovascular renal condition	11.2	10.5	8.06	0.20	+ 2.7	Vagotonic	5	9.8	198	36
40*	40	Changes in capillaries	10.8	6.6	8.70	0.39	+22	Vagotonic	0	5.8	201	40
40*	40	Changes in capillaries	10.2	6.6	8.70	0.39	+22	Vagotonic	0	5.8	201	40
96*	40	Cardiovascular renal condition	8.2	7	7.26	0.11	+31	Vagotonic	0	28.4	243	70
102*	40	Tuberculosis	10.6	5.8	7.95	0.20	+22	Vagotonic	0	18.2	170	66
140	40	Tuberculosis; glaucoma	11.4	4.05	6.77	0.45	.....	Vagotonic	0	30	...	45
15*	38	Healed tuberculosis	12.1	7.5	7.95	0.19	— 4.5	Sympathetic-otonic	12	12.4	210	60
26*	35	Syphilis	10.2	11	8.28	0.28	+ 9.6	Vagotonic	6.4	11.6	210	30
48*	35	Syphilis	9.6	9.7	8.59	0.10	8.3	Sympathetic-otonic	0	7	222	46
77*	35	Sensitized	10.8	10	6.98	1	7.9	Vagotonic	15.4	17	187	39
73*	35	Syphilis	11.2	7.6	8.5	2	16.3	Vagotonic	0	20	191	48
158	35	Hodgkin's disease	9.3	4	8.28	0.29	37	Sympathetic-otonic	0	22	173	49
42*	32	Cardiovascular renal condition	11.4	6.5	7.63	0.15	6.8	Vagotonic	4.6	5.8	241	33
80*	30	Nervous	8	15.1	8.28	1.6	13	Vagotonic	9.2	16.2	212	30
106*	30	Cardiovascular renal condition	11.2	12	8.06	0.63	— 6.6	Vagotonic	0	25.6	243	60
137	30	Glaucoma	8.1	4	8.49	1.9	3.6	Vagotonic	0	18	166	61
	38	Averages and totals	10.3	7.86	8.11	0.537	+12	15 V., 5 S.	3.9	19.96	204	49.3

* One of group of 100 "normal" men.

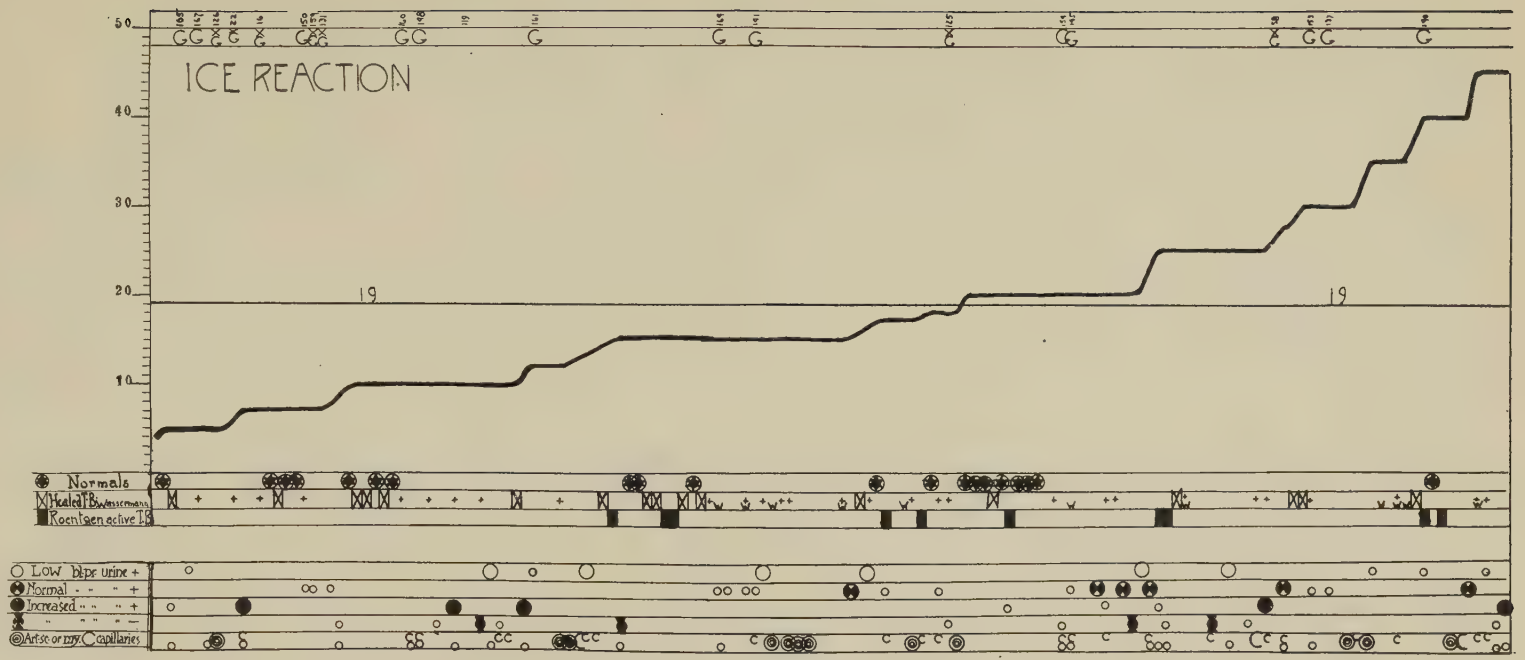

Chart 13.—The ice reaction time of normal persons and patients with various clinical conditions.

20 minutes). This group is composed of those persons who were noted for relatively low capillary permeability, and some of them show a sluggish capillary circulation.

The persons with roentgenologic evidence of active tuberculosis appear toward the side of the curve representing delay, and it seems that more of the group with cardiovascular renal conditions are found here. The advanced ages of the members of both these groups must be taken into consideration.

WEIGHT/LENGTH RATIOS

The average weight/length ratio (weight in pounds, length in inches) for our group of 100 "normal" men is 217 (chart 14). When we select the twenty persons with the highest ratios, it is evident that the group includes most of the persons in whose cases a roentgenologic diagnosis of myocarditis was made. The majority give a vagotonic reaction to epinephrine, and their K/Ca ratios average 2.06.

In part I, table 1, the correlations with the weight/length ratio indicate that as the ratio increases the capillary permeability diminishes, the K/Ca ratio increases, the sugar increases, the basal metabolic rate decreases, as also does the skin resistance, the pulse pressure on subcutaneous injection of epinephrine hydrochloride and the CO_2 combining power increase, and the wheal due to epinephrine and the flare due to morphine increase.

In tables 36 and 37, the averages for the sugar and the basal metabolic rate show little difference between the two extreme groups, but there are more persons with high skin resistance in the group with the highest ratios. The wheals due to epinephrine are larger here, as are the flares due to morphine, while the wheals due to thyroxin are smaller.

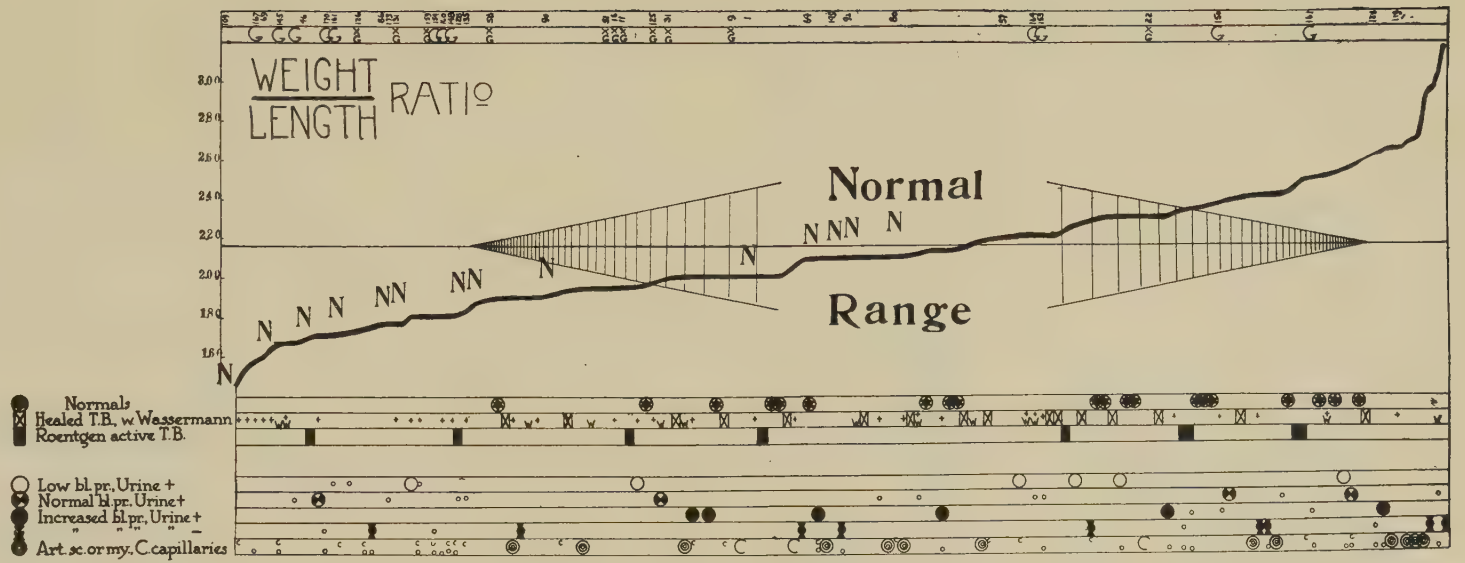

Chart 14.—The weight length ratio of normal persons and of patients with various clinical conditions.

TABLE 36.—*The Results of Examinations of the Twenty Persons with the Lowest Weight/Length Ratios*

Individual Number	Weight/Length Ratio	Diagnosis	K / Ca Ratio	Sugar, Mg.	Basal Metabolic Rate	Skin Resistance to Electric Current	CO_2 Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Morphine, Wheal, Mm.	Morphine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
174	143	Raynaud's disease	2	90	4	....	55	Vagotonic	0	. ..	....	....	....	....	....
109	140	Neurosis	1.5	67	.....	0.47	51.4	Vagotonic	3	18	9	9	7.2	12	9.4
147	142	Postencephalitis	2	79	— 6	0.54	57.9	Sympatheticotonic	8	18	11.6	12	7.4	13	0
118	154	Arthritis	1.4	80	—11	1.9	54.2	Vagotonic	— 8	16.8	7.4	10	6.8	12	8.6
167	158	Glaucoma	1.9	81	—13	0.85	47.9	Sympatheticotonic	+62	17	14.2	12	9	15	0
69	160	Ulcer; nervous	1.66	70	+ 4	1.9	54.8	Sympatheticotonic	0	21.2	10	12.2	22	14.4	10.2
171	161	Urticaria	1.42	72	8	0.08	48.7	Sympatheticotonic	12	17.5	10.5	12.5	0	18	0
145	166	Wassermann reaction +; glaucoma	1.55	70	19	0.35	55.4	Sympatheticotonic	43	18	13.6	16	0	16	0
172	163	Raynaud's disease	1.64	76	18	0.08	....	Sympatheticotonic	57	22.4	16	15.5	8.5	18	16
137	163	Glaucoma	2.24	73	3.6	1.9	51.9	Vagotonic	7	15.4	10.5	12.5	10	13	0
46*	168	Inanition	1.24	61	13	1.7	56.2	Sympatheticotonic	15	21.2	13.2	15	16.2	12.2	11
162*	170	Tuberculosis	1.63	62	22	0.20	60.9	Vagotonic	11	23.2	7.4	10.8	15	12.2	0
55*	170	Cardiovascular renal condition (urine)	3.1	73	6.2	0.38	56.6	Vagotonic	5	17.6	8.2	10.2	19.6	11.2	0
170	170	Glaucoma	2.2	320	33	0.07	52.5	.....	....	....	....	....	....	....	....
161	171	Glaucoma	1.93	86	16	1.4	49.4	Sympatheticotonic	25	14	13	5.5	10.7	13	0
120	172	Purpura	1.99	71	— 5	....	52.2	.....	....	21.2	7.2	9.6	8.2	12	0
158	173	Hodgkin's disease	2	83	+37	0.29	57.8	Sympatheticotonic	10	19.2	11.3	13	0	28	0
144	174	Pellagra	1.79	90	— 3.7	0.5	54.4	Sympatheticotonic	50	14.4	11.5	12.6	12.5	15	0
30*	175	Arteriosclerosis; cardiovascular renal condition	2.33	76	— 5.9	1.05	62.5	Vagotonic	0	20	8.8	8.2	16	7.2	0
86*	176	Nervous	1.26	94	+ 6.4	0.33	55	Vagotonic	—12	18	14	11.8	19.6	15.4	12.4
	163	Averages and totals	1.89	76	7.6	0.77	53.9	10 S., 8 V.	15	1.85	10.9	11.6	9.9	14.3	3.7

* One of group of 100 "normal" men.

TABLE 37.—*The Results of Examinations of the Twenty Persons with the Highest Weight/Length Ratios*

Individual Number	Weight/Length Ratio	Diagnosis	K / Ca Ratio	Sugar, Mg.	Basal Metabolic Rate	Skin Resistance to Electric Current	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Morphine, Wheal, Mm.	Morphine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
45*	317	Increased blood pressure (above 140)	1.48	77	20	0.28	Vagotonic	— 3	20.4	9.8	14.2	21.4	16.4	12
6	300	Arteriosclerosis; myocarditis	1.80	70	29	0.30	Vagotonic	0	....	....	....	....	....	....
121	294	Arthritis deformans	2.27	74	11	0.28	Vagotonic	—13	26	5.6	10.2	8.8	8	0
103*	270	Arteriosclerosis; myocarditis	1.88	57	2	0.39	Vagotonic	— 1	22.4	9	12.2	18.2	12.2	0
138	270	Myocarditis; Fröhlich's syndrome	1.88	83	8	0.07	Vagotonic	— 0	23	9.5	12.5	8.7	17	6.5
93*	267	Myocarditis; hay-fever	3.22	70	0	0.25	Sympatheticotonic	+19	20.4	8.6	12.4	15	10	0
119	266	Adenoma of the thyroid	2.1	75	34	0.08	Sympatheticotonic	+13	24	5	12	11.2	12	7
107*	265	Arteriosclerosis; myocarditis	2.3	60	—6.5	0.33	Vagotonic	— 1	20.8	5.8	8.6	11.2	13.4	6.2
70*	264	Arteriosclerosis; arthritis deformans	1.45	67	23	0.39	Vagotonic	— 6	18	11	9.8	18.2	10	0
123	263	Arteriosclerosis; carcinoma of the thyroid	2.17	81	48	....	Vagotonic	— 3	20	6.8	11.2	10.2	10	12.2
47*	260	Healed tuberculosis	2.51	72	34	0.13	Vagotonic	— 5	21.6	5.2	14.2	10.8	9	0
83*	258	Normal	2.31	68	—7	0.16	Vagotonic	+ 9.6	17.2	9.2	9.2	20.8	13.4	11
66*	257	Arteriosclerosis; myocarditis	1.82	67	1.3	0.37	Sympatheticotonic	+37	20	9.2	13.6	16.6	10.2	0
54*	256	Myocarditis	....	80	—3.4	0.26	Sympatheticotonic	+66	21.2	10.4	11	18	12	0
37*	254	Normal	2.26	75	—24.4	0.34	Vagotonic	— 8	20.4	21.6	18	15.2	10	0
39*	254	Syphilis	1.91	79	13.1	0.29	Vagotonic	+17	18	9.8	13.8	21.8	7.6	5
59*	252	Normal	1.88	85	—6.5	0.16	Vagotonic	+ 2	22	7.2	9.2	21.4	15.6	8
165	250	Arteriosclerosis; glaucoma	1.79	80	0.5	0.18	.....	.....	16.8	13	10	14.5	12.5	0
129*	249	Tuberculosis	1.65	83	+28	0.22	Vagotonic	—10	18.4	7	10.6	9.6	12.2	0
56*	247	Tuberculosis	2.52	65	+17.9	0.32	Vagotonic	+14	17.2	5.8	10.8	22.4	13.4	7
	265.6	Averages and totals	2.06	73.4	9.3	0.25	15 V., 4 S.	6.2	19.8	8.9	11.7	15.4	11.8	3.9

CHOLESTEROL

The determinations of cholesterol were made on 109 members of the groups of "normal" persons and patients, the average amount for the persons of the "normal" group being 207 mg.

In chart 15 we illustrate this material. Of the actually normal persons, we have only eight for consideration, and have placed the normal range at from approximately 160 to 245. Of this group, patient 92 falls far outside this range, having a cholesterol level of over 300.

Furthermore, it appears that the group with the higher levels of cholesterol includes more persons with roentgenologic evidence of

TABLE 38.—*The Results of Examinations of the Twenty Persons with the Highest Values of Cholesterol*

Individual Number	Cholesterol, Mg.	Diagnosis	Reaction to Epinephrine
95	318	Healed tuberculosis	Sympatheticotonic
148	317	Vitiligo; glaucoma	Vagotonic
94	303	Normal	Vagotonic
111	290	Cardiovascular renal condition	Sympatheticotonic
14	278	Cardiovascular renal condition	Vagotonic
75	278	Cardiovascular renal condition	Vagotonic
109	269	Neurosis	Vagotonic
141	267	Glaucoma	Vagotonic
173	267	Tumor of the cord	Sympatheticotonic
61	264	Cardiovascular renal condition	Vagotonic
62	256	Cardiovascular renal condition	Vagotonic
167	256	Glaucoma	Sympatheticotonic
107	256	Cardiovascular renal condition	Vagotonic
132	256	Eczema	Vagotonic
71	256	Cardiovascular renal condition	Vagotonic
136	256	Pellagra	Sympatheticotonic
115	247	Cardiovascular renal condition	Vagotonic
127	247	Cardiovascular renal condition	Sympatheticotonic
150	247	Glaucoma	Vagotonic
73	247	Syphilis	Vagotonic
Average.....	268	Total	6 S., 14 V.

healed parenchymal tuberculosis. In connection with the group with cardiovascular renal lesions, the outstanding fact seems to be that there are more persons with arteriosclerosis in the group with the high levels of cholesterol. This seems true for the 100 "normal" men, as well as for all the persons examined.

In tables 38 and 39, we have tabulated the results of some examinations of the twenty persons with the highest and lowest cholesterol values (excluding those with exophthalmic goiter). There are obviously more persons with arteriosclerotic changes and increased blood pressure on the side of the high values of cholesterol than on the side of the low values. It appears, too, that this group includes more persons with a distinctly vagotonic reaction to epinephrine.

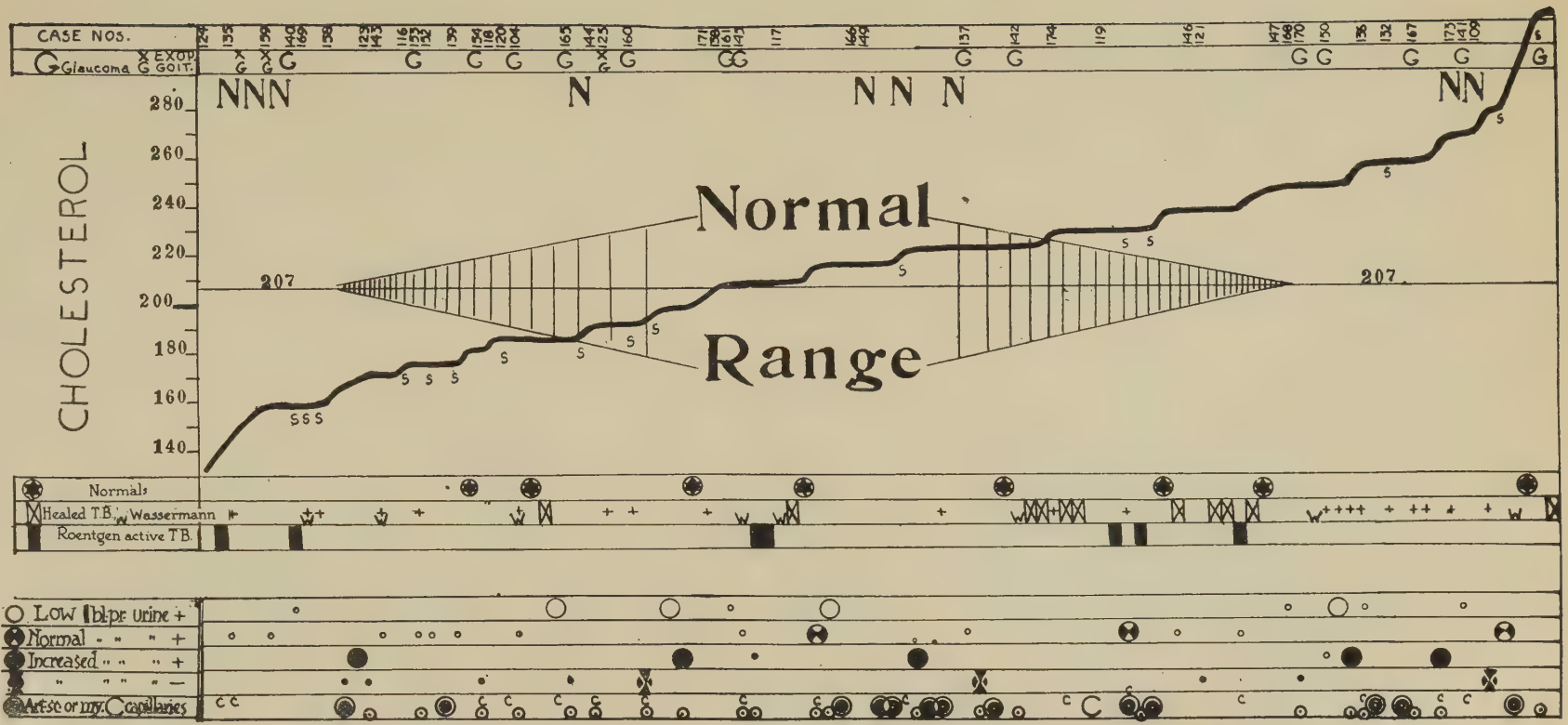

Chart 15.—The cholesterol content of the blood of normal persons and patients with various clinical conditions.

TABLE 39.—*The Results of Examinations Similar to Those in Table 38 of the Twenty Persons with the Lowest Values of Cholesterol*

Individual Number	Cholesterol, Mg.	Diagnosis	Reaction to Epinephrine
124	133	Heart disease and arthritis	Vagotonic
108	139	Tuberculosis	Sympatheticotonic
135	145	Nervous	Vagotonic
92	158	Nervous	Sympatheticotonic
1	158	Nervous	Sympatheticotonic
140	158	Tuberculosis; glaucoma	Vagotonic
169	158	Syphilis; Buerger's disease	Sympatheticotonic
101	158	Sensitized	Sympatheticotonic
158	163	Hodgkin's disease	Sympatheticotonic
96	167	Cardiovascular renal condition	Vagotonic
84	167	Cardiovascular renal condition	Sympatheticotonic
143	171	Pellagra	Sympatheticotonic
85	171	Fever, unknown origin	Vagotonic
116	175	Urticaria	Vagotonic
153	175	Glaucoma	Sympatheticotonic
152	175	Sensitized	Vagotonic
98	175	Cardiovascular renal condition	Vagotonic
139	175	Urticaria	Vagotonic
64	180	Normal (nervous)	Sympatheticotonic
154	180	Glaucoma	.....
Average.....	162	Total	10 S., 9 V.

REACTIVITY TO EPINEPHRINE: THE WHEAL

The average diameter of the wheals due to epinephrine of our group of 100 "normal" men is 19.2 mm., and there appear to be relations to the calcium level, the Kromayer lamp erythema time, the basal metabolic rate, the pulse pressure and the weight/length ratio.

TABLE 40.—*The Results of Examinations of the Twenty Persons Showing the Smallest Wheals on the Intracutaneous Injection of Epinephrine Hydrochloride*

Individual Number	Epinephrine, Wheal, Mm.	Diagnosis	Calcium, Mg.	Kromayer Light Erythema Time, Min.	Pulse Rate	Carbon Dioxide Combining Power	Ice Reaction Time, Seconds
135	12.4	Changes in capillaries; nervous	11.9	75	88	54.5	18
49*	12.4	Cardiovascular renal condition	11	330	60	59.1	15
81*	14	Cardiovascular renal condition	8.4	90	76	57	45
161	14	Glaucoma	9.17	75	88	49.4	12
77*	14	Sensitized	10.8	240	82	60.6	35
144	14.4	Pellagra	9.8	120	92	54.4	10
80*	14.8	Nervous	8	100	64	53.2	30
124	15.2	Arthritis	10.5	90	98	53.7	10
137	15.4	Glaucoma	8.1	130	78	51.9	30
65*	15.8	Cardiovascular renal condition	9.8	180	63	53.1	13
160	16	Glaucoma	10.86	70	68	62.7	10
87*	16	Normal	8.4	90	70	55.4	18
139	16	Urticaria	9.7	120	104	50	8
84*	16.4	Cardiovascular renal condition	10	90	80	53.1	20
143	16.6	Wassermann reaction +++; pellagra	9.7	110	118	55.4	15
118	16.8	Arthritis	12.2	110	72	54	12
24*	16.8	Healed tuberculosis	11.7	120	78	53.7	20
91*	16.8	Cardiovascular renal condition	....	150	76	58.9	45
165	16.8	Glaucoma	10	80	110	53.9	5
167	17	Glaucoma	12	120	84	47.9	5
Averages	15.5	.....	10.1	124	82	54.6	18.8

* One of group of 100 "normal" men.

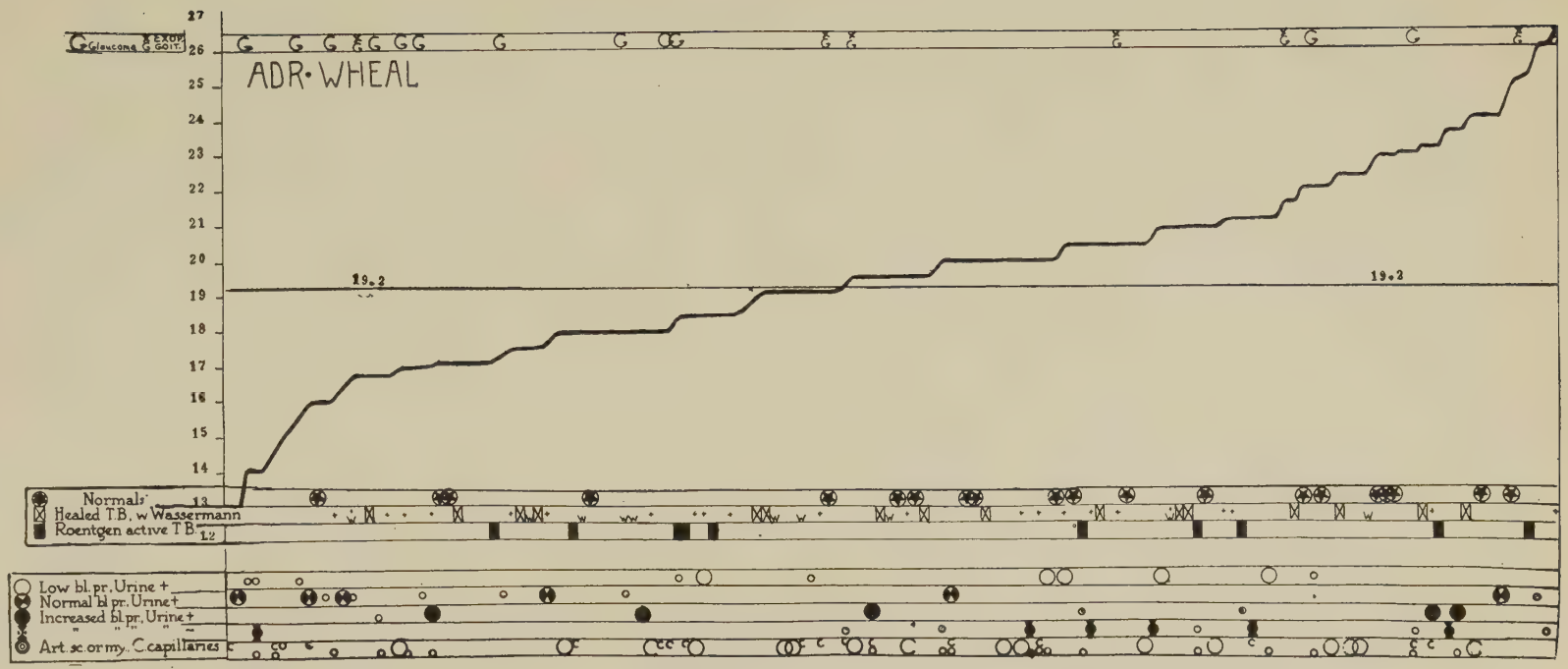

Chart 16.—The diameter of the wheal in the reaction to epinephrine of normal persons and patients with various clinical conditions.

TABLE 41.—*The Results of Examinations of the Twenty Persons Showing the Largest Wheals on the Intracutaneous Injection of Epinephrine Hydrochloride*

Individual Number	Epinephrine, Wheal, Mm.	Diagnosis	Calcium, Mg.	Sugar, Mg.	Kromayer Light Erythema Time, Min.	Basal Metabolic Rate	Blood Pressure, Systolic	Pulse Pressure	Pulse Rate	Vascular Reaction to Epinephrine	Epinephrine Pulse Pressure, % Increase	CO_2 Combining Power	Ice Reaction, Seconds	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.
121	26	Arthritis deformans	8.9	74	120	+11	148	68	88	Vagotonic	−13	56.8	10	8	0
152	26	Angioneurotic edema	9.8	63	60	+ 4.8	120	46	80	Vagotonic	— 5	63.4	15	9	8
20*	25.2	Tuberculosis	11.4	85	90	+20.4	130	54	80	Vagotonic	+13	62.7	15	10	2.6
50*	24.8	Normal	11.4	..	180	+21	128	58	67	Sympatheticotonic	+12	64.9	15	10.4	10
14*	24.4	Cardiovascular renal condition	11.2	67	90	+ 2.7	128	48	76	Vagotonic	10	65	40	15	5
41*	24.4	Normal	9.8	70	75	+15	110	36	64	Vagotonic	+26	58.6	7	6.2	0
40*	24	Changes in capillaries	10.8	56	75	+22	110	46	60	Vagotonic	+ 6	55.7	40	6.2	0
95*	23.6	Healed tuberculosis	7.8	77	110	+23	110	44	68	Sympatheticotonic	+ 9	61.6	10	12	6.2
134	23.6	Cardiovascular renal condition	9.9	71	80	— 4.4	148	62	78	Sympatheticotonic	— 0	54.8	12	19.2	9.6
32*	23.6	Cardiovascular renal condition	9.5	76	75	+22	144	58	74	Vagotonic	+22	54.1	25	9.8	0
21*	23.2	Cardiovascular renal condition	10.2	72	105	+ 4.3	140	56	72	Vagotonic	0	62.9	25	7.2	2.6
15*	23.2	Healed tuberculosis	12.1	70	90	— 4.9	128	60	60	Sympatheticotonic	+13	57.6	38	11.6	12
102*	23.2	Tuberculosis	10.6	62	90	+22	114	44	96	Vagotonic	+11	60.9	40	12.2	0
138	23	Fröhlich's syndrome	10.6	83	90	8	122	46	80	Vagotonic	....	55.2	17	17	6.5
154	23	Glaucoma	....	71	90	18	194	76	70	.....	....	56.6	20	26	0
35*	22.8	Normal	8.7	79	75	12.3	108	30	62	Vagotonic	+33	57.6	20	9.2	0
29*	22.8	Normal (bile in urine)	10	76	195	3.5	134	46	76	Sympatheticotonic	+24	60.1	15	7.2	0
4*	22.8	Normal	11.8	94	120	12	114	34	80	Sympatheticotonic	+21	64.3	20	10.2	0
172	22.4	Ravnaud's disease	13	76	105	18	108	30	94	Sympatheticotonic	+57	....	45	18	16
153	22	Glaucoma		83	90	2	124	64	64	Sympatheticotonic	+10	73.2	30	18	0
	23.8	Averages and totals	10.3	74	99	11.7	128	50	74	8 S., 11 V.	+12	60	22.9	12	3.9

* One of group of 100 "normal" men.

When we include our entire material and examine the results, some of these correlations are maintained. The differences in calcium levels are not marked, but the Kromayer lamp erythema time is shortened in the group with the larger wheals and the difference between the groups in the CO_2 combining power is well marked, as is that in the ice reaction time (tables 40 and 41).

There are no apparent correlations with blood sugar level, the blood pressure, the pulse pressure or the vascular reactions to epinephrine. The pulse rate is somewhat increased in the group with the smaller wheals.

Chart 16 shows the truly "normal" persons scattered over the entire length of the curve. There appear to be no correlations with the cases of healed or active tuberculosis (roentgenologic evidence) nor with the cardiovascular renal conditions.

REACTIVITY TO EPINEPHRINE: THE FLARE

The flare from epinephrine is, as has been shown in chart 1, correlated with a number of other reactions. Thus, it is larger in persons with more calcium, more sugar, higher skin resistance, less globulin and greater vascular reaction to epinephrine. The reactions to thyroxin are not closely related, but the flare due to morphine increases with increase in the flare due to epinephrine.

These observations made on the "normal" group are all confirmed when our averages include the clinical material. In tables 42 and 43, the corresponding results are tabulated for the groups with the greatest and the smallest flares. It will be noted, among other things, that there are more persons with primarily sympatheticotonic reactions in the group with the large flares.

Chart 17 indicates that our truly "normal" group, as well as the group showing roentgenologic evidence of healed tuberculosis, are scattered over the entire curve, while more of the group with roentgenologic evidence of active tuberculosis appear at the lower end of the curve. The groups with cardiovascular renal conditions offer nothing that is characteristic, but the group with exophthalmic goiter appears to have smaller flares in contradistinction from the group with glaucoma. The "nervous" persons apparently are more apt to have large flares.

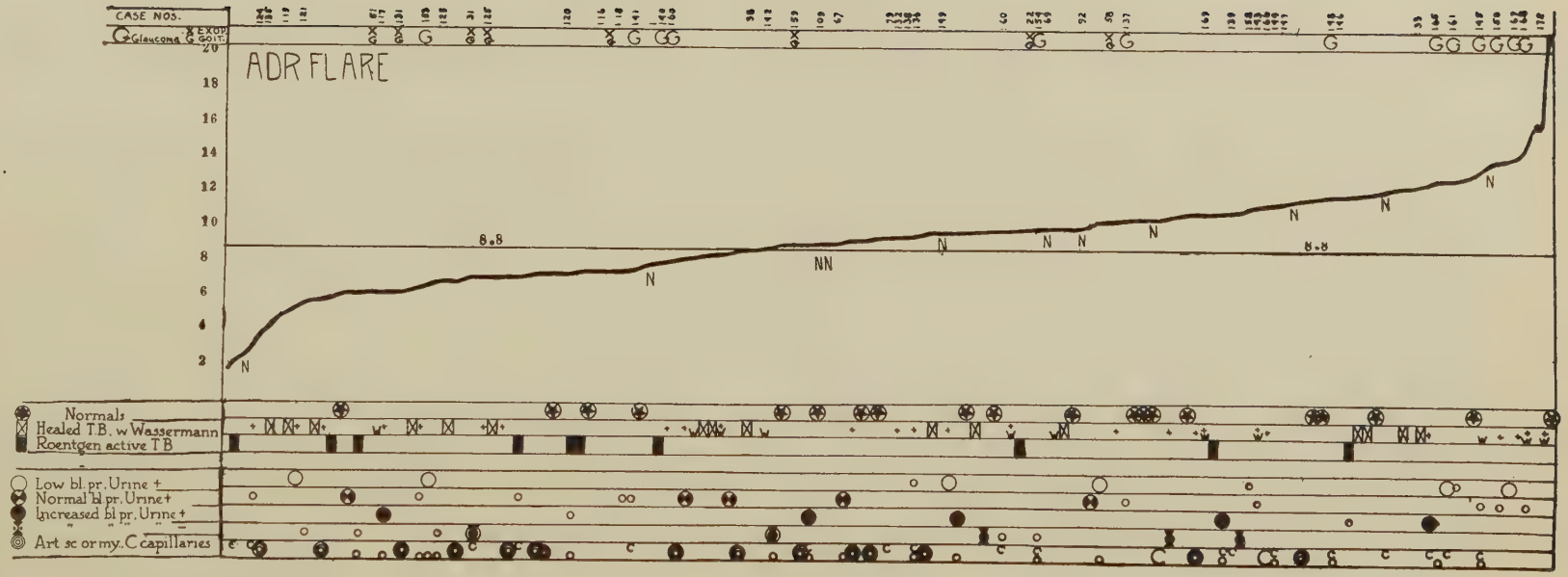

Chart 17.—The radius of the flare in the reaction to epinephrine of normal persons and patients with various clinical conditions.

TABLE 42.—*The Results of Examinations of the Twenty Persons Showing the Smallest Flares Following the Intracutaneously Injection of Epinephrine Hydrochloride*

Individual Number	Epinephrine, Flare, Mm.	Diagnosis	Calcium, Mg.	Sugar, Mg.	Globulin, Mg.	Skin Resistance to Electric Current	Blood Pressure, Systolic	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheal, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Morphine, Flare, Mm.
85*	1.8	Fever	10.6	79	33	0.41	110	Vagotonic	+19	17.2	14.2	0	13.8
108*	2.4	Tuberculosis	10.4	63	50	0.44	94	Sympathetic-cotonic	+ 9	18	14.8	13.2	11
124	2.6	Heart disease; arthritis.	10.5	71	40	1.05	122	Vagotonic	+ 2	15.2	....	....	6.8
135	3.2	Nervous	11.9	75	45	0.09	120	Vagotonic	—10	12.4	20	....	2
98*	4	Cardiovascular renal condition	8.8	63	42	0.20	136	Vagotonic	+ 6	20	11.2	0	3
110*	4.2	Healed tuberculosis	12.1	61	28	0.60	110	Vagotonic	— 4	20.8	12	9.4	14.6
47*	5.2	Healed tuberculosis	10.4	72	40	0.13	136	Vagotonic	— 5	21.6	9	0	10.8
130*	5.4	Cardiovascular renal condition	10.4	86	60	0.35	106	.....	....	20	11.2	0	12.6
121	5.6	Arthritis deformans	8.9	74	30	0.28	148	Vagotonic	—13	26	8	0	8.8
101*	5.6	Healed tuberculosis	9	52	38	0.09	118	Vagotonic	26	19.6	12	10.4	16
107*	5.8	Cardiovascular renal condition	8	60	40	0.33	134	Vagotonic	— 1	20.8	13.4	6.2	11.2
56*	5.8	Tuberculosis	9.8	65	35	0.32	124	Vagotonic	+14	17.2	13.4	7	22.8
94*	6	Normal	8.4	75	37	0.43	134	Vagotonic	20	20	11.2	7.8	14
14*	6.2	Tuberculosis	7.4	55	45	0.08	176	Vagotonic	11	20.8	12	0	10
104*	6.2	Cardiovascular renal condition	11.2	67	37	0.20	128	Vagotonic	0	24.4	15	5	7.2
117	6.2	Syphilitic arthritis	9.2	60	27	0.25	130	Sympathetic-cotonic	6	19.2	20.2	0	6.2
115*	6.2	Cardiovascular renal condition	7.8	60	60	0.28	148	Vagotonic	— 4	17.2	14.2	8	13.2
81*	6.4	Healed tuberculosis	7.8	77	30	0.39	110	Sympathetic-cotonic	+ 9	23.6	12	6.2	12.6
95*	6.2	Cardiovascular renal condition	8.4	63	37	0.10	144	Vagotonic	+ 4	14	10	0	15
153	6.5	Glaucoma	9	83	0	0.15	124	Sympathetic-cotonic	+10	22	18	0	0
	5.07	Averages and totals	9.5	68	39.7	0.308	127.6	4 S., 15 V.	+ 4	195	13	4	10.5

* One of group of 100 "normal" men.

TABLE 43.—*The Results of Examinations of the Twenty Persons Showing the Largest Flares Following the Intracutaneous Injection of Epinephrine Hydrochloride*

Individual Number	Epinephrine, Flare, Mm.	Diagnosis	Calcium, Mg.	Sugar, Mg.	Globulin, Mg.	Skin Resistance to Electric Current	Blood Pressure, Systolic	Vascular Reaction to Epinephrine	Epinephrine, Pulse Pressure, % Increase	Epinephrine, Wheal, Mm.	Morphine, Flare, Mm.
37*	12.6	Epilepsy	9.5	83	45	1.75	122	Sympathetic-cotonic	+ 2	20	22.2
172	16	Raynaud's disease	13	76	..	0.08	108	Sympathetic-cotonic	+57	22.4	8.5
168	16	Orthostatic albuminuria	9.4	45	13	0.16	105	Vagotonic	+ 4	18	0
164	14.7	Wassermann reaction +; glaucoma	8.7	65	20	0.23	110	Sympathetic-cotonic	+14	18	7.5
167	14.2	Glaucoma	12	81	27	0.85	137	Sympathetic-cotonic	+62	17	9
36*	14.2	Cardiovascular renal condition	12.1	90	33	0.11	104	Vagotonic	22	20.8	18
150	14	Glaucoma	12	82	15	0.22	140	Vagotonic	+ 6	17	9.5
86*	14	Nervous	12.6	94	40	0.36	118	Vagotonic	—12	18.8	19.6
45	13.6	Glaucoma	10.1	70	55	0.35	136	Sympathetic-cotonic	+43	18	0
41*	13.2	Normal	9.8	70	50	0.26	110	Vagotonic	+26	24	18.8
46*	13.2	Inanition	13.8	61	30	1.7	140	Sympathetic-cotonic	+15	21.2	16.2
161	13	Glaucoma	9.17	86	20	1.4	108	Sympathetic-cotonic	+25	14	17.5
65*	13	Cardiovascular renal condition	9.8	65	36	0.80	100	Sympathetic-cotonic	+30	15.8	19.8
165	13	Glaucoma	10	80	16	0.18	170	.....	....	16.8	14.5
21*	12.6	Cardiovascular renal condition	10.2	72	20	0.74	140	Vagotonic	0	23.2	13.6
15*	12.6	Healed tuberculosis	12.1	70	20	0.19	128	Sympathetic-cotonic	13	23.2	12.4
33	21.6	Normal	10	75	42	0.34	116	Vagotonic	— 8	20.4	15.2
24*	12.6	Healed tuberculosis	11.7	81	60	0.19	116	Sympathetic-cotonic	50	16.8	27.2
173	12.5	Tumor of the cord	10.5	80	6	0.09	106	Sympathetic-cotonic	23	21	0
80*	12.4	Nervous	8	69	33	1.60	116	Vagotonic	+ 7	14.8	19.2
	13.95	Averages and totals	10.7	74	30	0.562	121.5	11 S., 8 V.	+20	19	13

* One of group of 100 "normal" men.

REACTIVITY TO THYROXIN: THE WHEAL

The size of the wheal due to thyroxin, as has been shown in table 1, is related to the inflammatory index, to the potassium level and to the K/Ca ratio, as well as to the amounts of the globulins.

When we examine the inclusive material, we find these conclusions confirmed, as becomes evident from a survey of the results of the examinations in twenty cases of the smallest and twenty of the largest wheals (tables 44 and 45).

Chart 18 shows the wide range of the purely normal as well as of the groups with roentgenologic evidence of healed tuberculosis, but also makes evident the fact that the groups with roentgenologic evidence of active tuberculosis are apt to have the larger wheals.

The cardiovascular renal groups show no clear-cut relation, unless it is that the arteriosclerotic changes have not been made apparent in those with the small wheals.

TABLE 44.—*The Results of Examinations of the Twenty Persons Showing the Smallest Wheals Following the Intracutaneous Injection of Thyroxin*

Individual Number	Thyroxin, Wheal, Mm.	Diagnosis	Inflammatory Index	Potassium, Mg.	K / Ca Ratio	Globulin, Mg.
49*	4.2	Cardiovascular renal condition	11	25.2	2.29	17
116	5	Urticaria	17	19.4	1.94	40
33	5.4	Epilepsy	10	26.1	2.73	45
64*	6.2	Nervous	10	16.6	1.84	22
41*	6.2	Normal	9.1	21.2	2.16	50
40*	6.2	Changes in capillaries	6.6	18.7	1.73	44
90*	6.2	Nervous	7.6	14.5	1.34	33
3*	6.4	Healed tuberculosis	11.1	16.7	1.47	23
24*	6.6	Healed tuberculosis	11.6	24.8	2.12	60
26*	7.2	Syphilis	11	26.6	2.61	35
29*	7.2	Normal (bile in urine)	10.7	23.9	2.39	50
23*	7.2	Healed tuberculosis	11.1	28.6	2.19	..
21*	7.2	Cardiovascular renal condition	9	25.6	2.51	20
34*	7.2	Changes in capillaries	7.7	27.7	2.89	25
28*	7.4	Healed tuberculosis	10.6	24.1	2.19	42
36*	7.4	Cardiovascular renal condition	7.2	26.3	2.17	33
39*	7.6	Syphilis	5.8	18	1.91	43
48*	8	Syphilis	9.7	27.6	2.87	40
121	8	Arthritis deformans	11.5	20.2	2.27	30
79*	8.2	Ulcer	5.7	20	1.78	50
Averages	6.75		9.7	22.5	2.17	36.9

* One of group of 100 "normal" men.

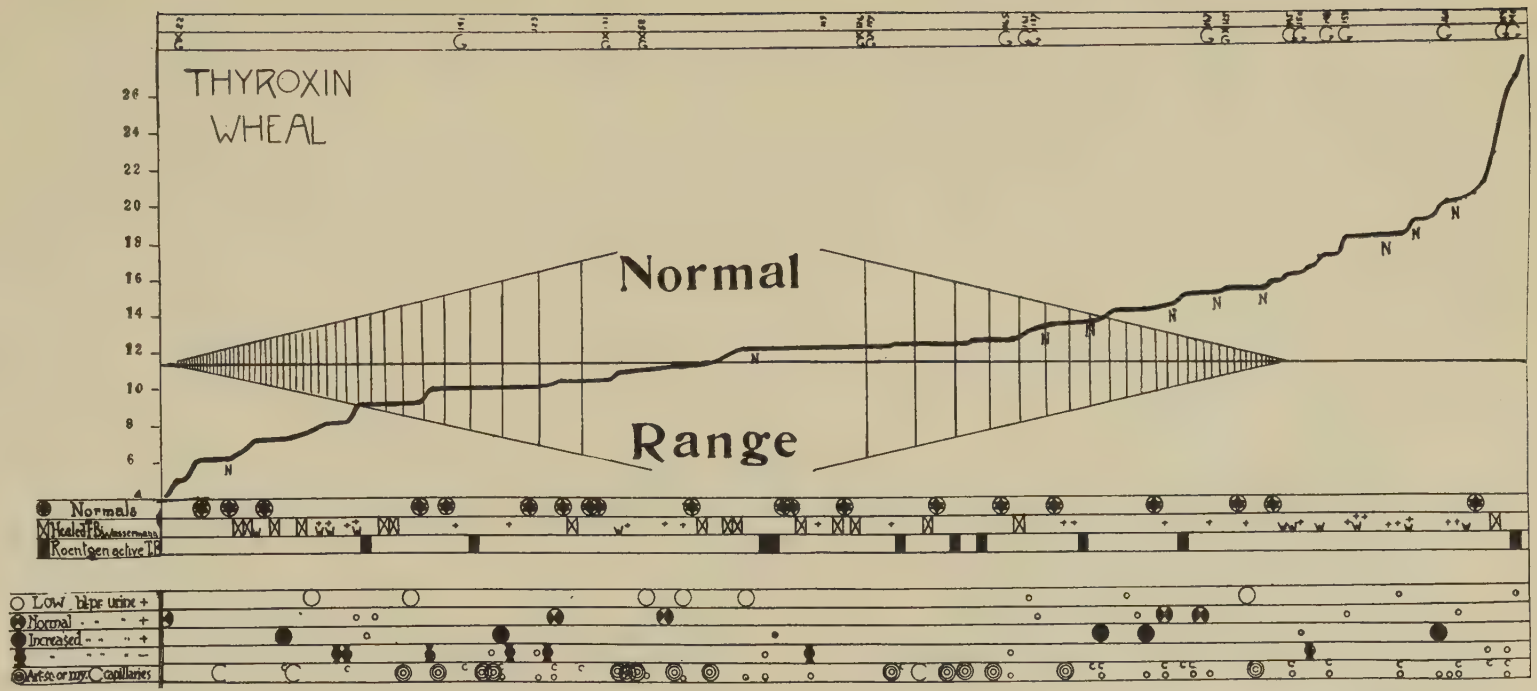

Chart 18.—The diameter of the wheal in the reaction to thyroxin of normal persons and patients with various clinical conditions.

TABLE 45.—*The Results of Examinations of the Twenty Persons Showing the Largest Wheals Following the Intracutaneous Injection of Thyroxin*

Individual Number	Thyroxin, Wheal, Mm.	Diagnosis	Permeability of Capillaries Ratio	Inflammatory Index	Potassium, Mg.	K / Ca Ratio	Globulin, Mg.
158	28	Hodgkin's disease	61	4	18.53	2	17
140	27	Tuberculosis; glaucoma	68	4	29.7	2.6	37.5
154	26	Glaucoma	60	4	23.08	....	3
13*	22.6	Healed tuberculosis	64	8	23.8	2.48	20
60	21	Cardiovascular renal condition	..	....	17.5	1.53	40
17*	20.6	Normal	66	8.2	18.2	1.43	17
117	20.2	Syphilitic arthritis	61	10	17.5	1.8	27
135	20	Nervous	84	14	19.6	1.65	45
160	20	Glaucoma	66	4.4	21.58	1.98	44
134*	19.2	Cardiovascular renal condition	60	4	15.4	1.56	42
146	19	Myasthenia	75	5	14.4	1.56	32
149	19	Nervous	54	5.4	17.4	1.74	0
172	18	Raynaud's disease	72	6	21.3	1.64	....
136	18	Cardiovascular renal condition; pellagra	74	5	18.8	1.88	35
173	18	Tumor of the cord	57	8	21.3	1.57	6
166	18	Eosinophilia	57	8	20.6	2.27	8
171	18	Urticaria	64	10	21.37	1.69	....
169	18	Wassermann reaction +++; Buerger's disease	62	4.1	19.24	1.56	20
153	18	Glaucoma	76	5	18.7	2.08	0
138	17	Fröhlich's (?) syndrome	73	12	19.9	1.88	11
Averages	20.2		66	6.7	19.88	1.83	25.2

* One of group of 100 "normal" men.

REACTIVITY TO THYROXIN: THE FLARE

In seventy-five persons, the intracutaneous injection of thyroxin produced no flare. This group includes the majority of the persons with glaucoma (eleven). Among those with flares, the "nervous" persons are numerous. No tables based on extremes have been prepared because of the large number of those with negative reactions (chart 19).

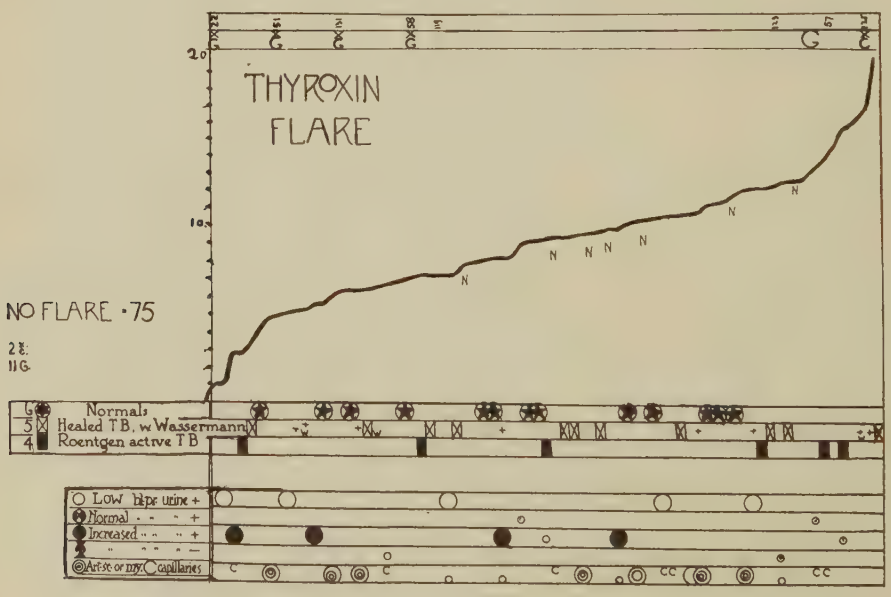

Chart 19.—The radius of the flare in the reaction to thyroxin of normal persons and patients with various clinical conditions.

IV. THE RELATION OF THE REACTION TO EPINEPHRINE TO THE POTASSIUM/CALCIUM RATIO AND TO OTHER RATIOS*

During the course of investigations dealing with a correlation of skin reactions with the blood chemistry and certain cardiovascular renal reactions, we have had occasion to study the effect of subcutaneous injections of epinephrine on the blood pressure of one hundred so-called "normal" men, as well as on about fifty patients who were ill from various diseases (glaucoma, exophthalmic goiter and other conditions). It is our purpose to enter into an analysis of these correlations in this paper.

It is agreed, we believe, that the original efforts of Eppinger and Hess [1] to classify all persons into groups that were vagotonic or sympathicotonic proved unsatisfactory, indeed confusing. There is no doubt that the emphasis placed on the study of the autonomic reactions of the patient has contributed immensely to the concept of the underlying factors of a number of disease conditions, but this study has added, for the time being at least, much uncertainty as well. Some of the confusion is due to the earlier concept that the autonomic apparatus consists merely of an equilibrated nervous mechanism with antagonistic impulses; to the pharmacologic aspect which has probably not infrequently failed to distinguish between direct protoplasmic action and selective action of the so-called autonomic drugs; to the fact that the cardiovascular response to epinephrine, for instance, need not be a criterion of its effect on other tissues. The great dependence of the reaction of individual organs or tissues on their state of activity when the autonomic impulse might become operative; the importance of the endocrine and humoral ionic milieu has been almost wholly disregarded. We seem warranted in believing at present that the original idea of Eppinger and Hess as to a one-sided preponderance of either the vagus or sympathetic nerve is incorrect; indeed, that when alterations do occur in the autonomic apparatus, both vagus and sympathetic nerves are involved; that when an apparent overbalance exists, overcorrection is usually apparent either in the organ or in remote regions; and that we deal not merely with an autonomic apparatus as such, but with more fundamental

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*Article by Petersen, W. F.; Levinson, S. A., and Arquin, S., reprinted from Arch. Int. Med. **42**:256 (Aug.) 1928.

1. Eppinger, H., and Hess, L.: Ztschr. f. klin. Med. **68**:205, 230, 1909.

alterations in the cells of the organs, changes intimately associated with stimulation or rest, fatigue or even death.[2]

Partly as a result of the indefinite clinical observations which have been associated with the so-called vegetative neuroses, clinicians in general make little use of the tests designed to elucidate the preponderance of either vagus or sympathetic influence, except in the study of the cardiac reactions. But in recent years the study of the electrolytes of the body, originating with Loeb and carried out in clinical directions particularly by the Kraus school [3] (Zondek, Arnoldi, Wollheim, Dresel, Kylin) and others, has indicated the intimate connection between the presumptive autonomic reactions, the electrolyte balance and the hormones. Kylin, in particular, has devoted considerable time to the correlation of these alterations in the blood chemistry in asthma, hyperpiesis, diabetes and other conditions to the reaction of epinephrine.[4]

As stated in the foregoing paragraphs, our material consisted, first, of a group of one hundred normal persons. Of these, about twenty were laboratory workers, the rest were men sent to us from an employment bureau. They were normal in the sense that they were not patients, and that they gave a cross-section of a male working population of varying ages. On closer analysis, however, the great majority were by no means absolutely normal. Of the total number, twenty-six were apparently normal in every sense; thirteen were apparently normal, but a well defined healed parenchymal tuberculosis was revealed by roentgen-ray examination. Then there were those cases in which active pulmonary tuberculosis was made probable by the roentgenogram, the cases with a positive Wassermann reaction, the markedly nervous persons, and a large group of persons who revealed cardiovascular-renal alterations, as shown by the blood pressure, roentgen-ray examination of the heart and large vessels, observations on the urine, microscopic examination of the capillaries of the skin, etc.

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2. Because of the confusion resulting from the conflicts between anatomic nomenclature and classification of the autonomic nervous apparatus and the pharmacologic methods of analysis, Müller and one of us (W. F. P.) (Arch. Int. Med. **40**:575 [Nov.] 1927) have used the term sympathetic status to denote organ activity associated with contracted vessels (i. e., usually tissue rest), while we have used the term parasympathetic status to denote tissue activity when the vascular channels are dilated (i. e., with stimulation of an organ). This is, of course, a purely functional point of view, but one which we believe avoids certain of the present difficulties.

3. Kraus, F. in Zondek, S. G.: Elektrolyte, Ihre Bedeutung für Physiologie, Pathologie und Therapie, Berlin, Julius Springer, 1927.

4. Kylin, E.: Acta med. Scandinav. **66**:197-206, 1927.

To this so-called normal material, there has been added a group of forty-nine patients from the wards of the Research Hospital. As so constituted there were:

Normal persons	26
Normal, with healed parenchymal tuberculosis	13
	39
Cardiovascular renal abnormalities	68

Among these were: 7 with glaucoma
5 with active tuberculosis
2 who were nervous
1 with syphilis
1 with urticaria
1 with angioneurotic edema

Nervous or neurasthenic	9
Angioneurotic edema	1
Syphilitic	5
Tuberculous	5
Exophthalmic goiter	7
Eczema	2
Epilepsy	1
Scleroderma	1
Myasthenia gravis	1
Urticaria	1
Heart disease	1
Epidemic encephalitis	1
Cancer of the thyroid	1
Glaucoma	2
Bronchitis	1
Feminine type young male	1
Dwarf	1
Tumor of the brain	1
Total	149

With some unavoidable degree of arbitrariness, we have divided these persons into ten groups according to the reaction of the systolic blood pressure following the subcutaneous injection of 0.5 cc. of a 1 : 1,000 dilution of epinephrine. In the individual curves which are presented, the systolic blood pressure curve for one hour after the injection is shown.

The first five groups can be regarded as sympathetic in character. Seventy-six persons are represented in these groups.

The second series can be classified as parasympathetic, in that either the reaction was negative, or showed a depressor action, either primary or permanent. There were seventy-three in these groups.

In examining the charts and tables, it may be of interest to note that so-called normal persons are found in both the sympathetic and the parasympathetic groups, but there are more in the sympathetic groups. No normal person has responded with a marked or persistent fall in blood pressure. It may also be of interest to note that twice as many of the extuberculous persons (as shown by roentgen-ray examination) are to be found in the sympathetic groups.

In table 3 are presented the averages of results of the observations in the ten groups for the various examinations that were made on the persons examined.

TABLE 1.—*Group of Persons Who Give Sympathetic Reactions*

Group	Number in Group	Type of Reaction	Normal	Ex. Tuberculosis	Cardiovascular Renal Disease
I	16	Immediate and sustained increase	1	3	9
II	19	Immediate increase, not sustained	3	0	8
III	15	Slow, sustained increase	3	3	6
IV	10	Slow rise, not sustained	2	1	7
V	16	Slight increase	6	2	6
Total...	76		15	9	36

TABLE 2.—*Group of Persons Who Give Parasympathetic Reactions*

Group	Number in Group	Type of Reaction	Normal	Ex. Tuberculosis	Cardiovascular Renal Disease
VI	24	Slight decrease	4	1	11
VII	14	More marked, slow decrease	0	0	8
VIII	14	First reaction down, recovery	3	0	4
IX	11	Similar to VIII	3	2	5
X	10	More marked primary drop, recovery	1	1	4
Total...	73		11	4	32

In table 4 A, the averages for the sympathetic groups (I-V) and the parasympathetic groups (VI to X) are shown. In these summaries, it will be noted that: (1) the amount of serum calcium and potassium is increased in the sympathetic group, but the ratio remains unchanged; (2) the albumin-globulin ratio is lower in the sympathetic group; (3) the Kromayer time is somewhat prolonged; (4) the electrical resistance of the skin is higher; (5) the reactions to epinephrine (as computed mathematically) are, of course, higher in the sympathetic group; (6) the subjects are proportionally lighter in weight.

As there are relatively many nonreactive persons in each group, we have narrowed the selection of the material to the groups more strikingly different, and for this purpose have taken groups I, II and III for the sympathetic and groups VII and X for the parasympathetic types. These groups contain fifty and twenty-four persons, respectively.

TABLE 3.—*Average Results of Examinations Made on Individuals in Ten Groups* *

Number in Group	Group	Blister Time (a)	Permeability (a)	Inflammatory Index (a)	Calcium	Potassium	Potassium-Calcium Ratio	Sugar	Albumin/Globulin (b)	Kromayer Time (c)	Basal Metabolism	Skin Resistance (d)	Muscle Reaction (e)	Blood Pressure	Pulse Rate	Reaction to Epinephrine, P. P. (f)	Reaction to Epinephrine, P. P. × P. R. (g)	Carbon Dioxide	Reaction to Ice (h)	Age	Wt. /.Lt. (i)	Cholesterol	(j) Epinephrine, White	Epinephrine, Red	Morphine, White	Morphine, Red	Thyroxin, White	Thyroxin, Red	Caffeine, White	Caffeine, Red
																	Sympathetic Group													
16	1	9.1	67	8.7	10.6	18.8	1.8	74	2.1	1.8	8.6	0.43	4	120/70	78	22	25.5	55.5	21	45.5	194	202	20	10	11.6	10.8	14	4	21	2
19	2	8.8	63	8.3	9.7	20.2	2.08	72	1.9	2.3	7.3	0.55	4.8	127/63	78	14	25	57.7	18	42	206	216	19.2	8.6	11.4	13.4	11.6	3.6	18.4	1.8
15	3	7.3	66	9	10.2	22.7	2.22	77	1.5	2	8	0.39	2.5	122/67	76	25	36	57.8	19	41	215	223	20	8.8	10.8	16	13.2	5.4	16.6	2.4
10	4	8.3	61.5	8.4	9.98	17.4	1.74	67	2.25	2.3	12.1	0.61	1.5	113/67	76	20	31.2	58.1	15	47.9	207	203	19.6	9.4	11.8	14.2	13	6.4	19.2	2.4
16	5	7	65	10.1	10.5	20.5	1.97	71	2.4	1.75	13	0.72	3.4	125/66	75	12	19	57.4	19	37.5	193	220	20	8.8	11	16	11.4	4.6	16	2.8
																	Parasympathetic Group													
24	6	7.3	64	9.5	10.3	20	1.97	73	2.2	1.83	9.5	0.46	2.3	110/67	78	5	6	58	21	40	217	204	19.2	8.6	11	14	12.4	4.4	18.8	3.4
14	7	7.8	63	9	10	19.6	1.99	73	2.1	1.75	9.7	0.46	2.4	133/66	77	5	6	57	22	47.7	227	204	20	8.8	10.2	13.6	9.4	3.2	19.2	1.8
14	8	8.1	63	8.6	9.5	18.8	1.86	76	2.5	1.96	9.6	0.46	3.6	120/70	76	7.5	19	57.3	14	42	206	226	19.6	9.6	12.8	12.4	10.8	5.2	16.8	3.4
11	9	6.5	64	10	10.1	19.9	1.97	74	2.4	1.76	11	0.25	4.6	130/75	74	12.4	23	56.4	16	42.4	230	240	20	8.6	12.4	16.4	11.2	4.8	16.4	4
10	10	9.1	58	7.4	9.3	19.6	2.08	71	2.2	1.58	19	0.25	4	134/74	69	9.6	15.5	59.7	16	55.7	213	227	18	8.6	10.68	9.4	13.6	2.52	23.2	1

* a, blister time– time in hours for formation of blister on forearm following cantharides plaster; permeability- ratio of protein in blister to protein in capillary blood; inflammatory index permeability divided by blister time in hours, Petersen, Wm. F., and Willis, D. A.: Arch. Int. Med. **38**: 663 (Nov.) 1926. b, method of Rohrer (Deutsches Arch. f. klin. Med. **121**: 221, 1916). c, time in hours of first appearance of erythema following a 30-second exposure of the forearm to Kromayer lamp. d, resistance of skin of the forearm to passage of electrical current. e, muscle reaction (cathodal closing contraction) in milliamperes. f, average increase or decrease in pulse pressure (in percentage of preinjection level) for one hour after injection. g, average increase or decrease in pulse pressure times pulse rate (in percentage of preinjection level) for one hour after injection. h, appearance time of erythema (in seconds) following transient application of ice to the chest wall. i, weight in pounds divided by length in inches. j, average side of wheal and flare (in mm.) following intracutaneous injection of epinephrine, 1:1,000,000, 1:100,000, 1:10,000, 1:1,000; morphine, 1:10,000,000, 1:1,000,000; thyroxin, 1:10,000; caffeine, 1:100.

In table 4B, it will be noted that the sympathetic group becomes more permeable, remains high in calcium and potassium content and retains the other differences previously noted. In addition, differences make their appearance in blood pressure, in the reaction to ice and in the red flare of the skin reactions.

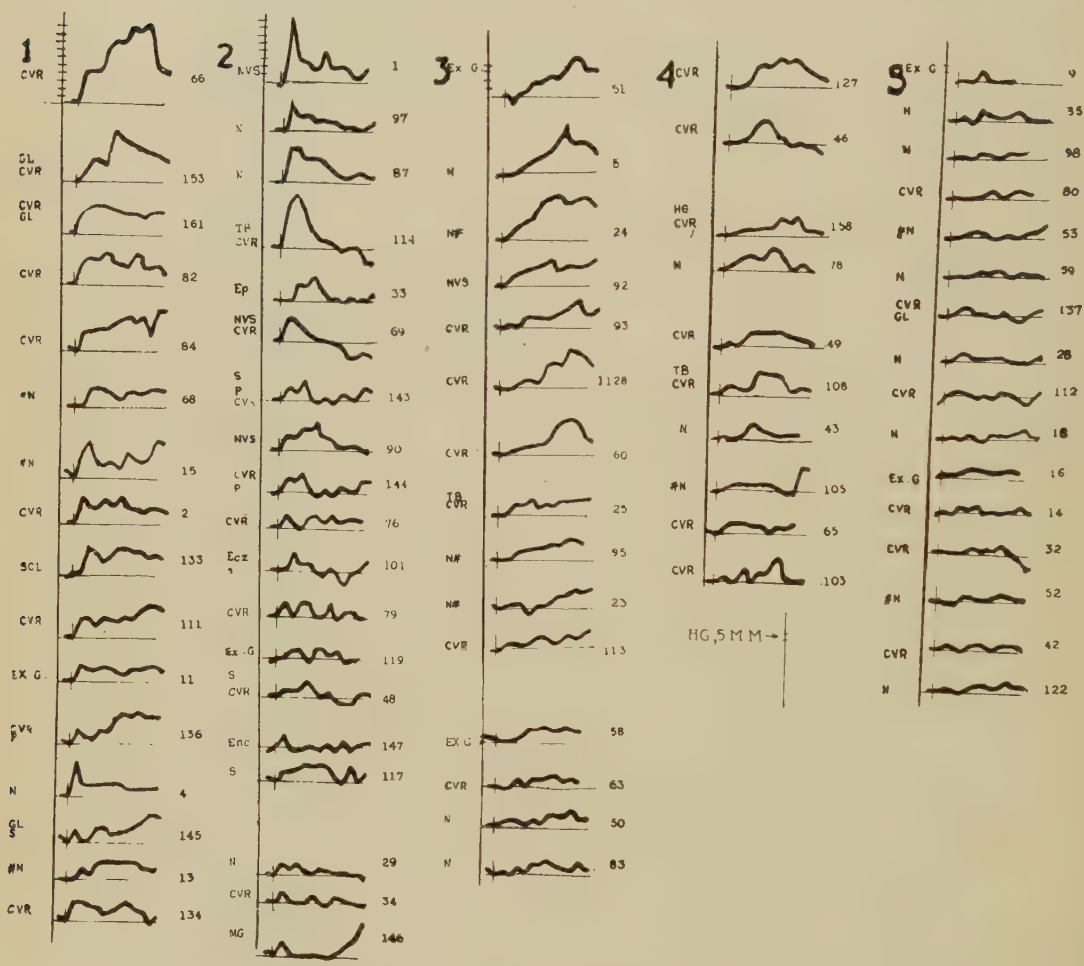

Fig. 1.—Graphic records of systolic blood pressure of sympathetic groups Numbers at the right indicate the patient's number. The abbreviations at the left indicating diagnosis, represent the following: *N*, normal; *#N*, normal but roentgen-ray evidence of healed parenchymal tuberculosis; *C.V.R.*, cardiovascular renal complication; *Gl*, glaucoma; *Scl.*, scleroderma; *Ex.G.*, exophthalmic goiter; *P.*, pellagra; *S.*, syphilis; *N.V.S.*, nervous neuraesthenia; *T.B.*, tuberculosis; *Ep.*, epilepsy; *Ecz.*, eczema; *Enc.*, encephalitis; *M.G.*, myasthenia gravis; *HG*, Hodgkin's disease; *Urt.*, urticaria; *Ang. Neu. Ed.*, angioneurotic edema; *H. D.*, heart disease; *N. S.*, normal, sensitized; *G.*, glandular, feminine type; *Ca Thy.*, carcinoma thyroid; *D.*, dwarf; *F.*, fever, bronchitis.

We can go one step farther and select ten of the outstanding cases of each series and examine their averages. The cases selected include the first ten of group I and the last ten of group VII. The average are recorded in table 4.

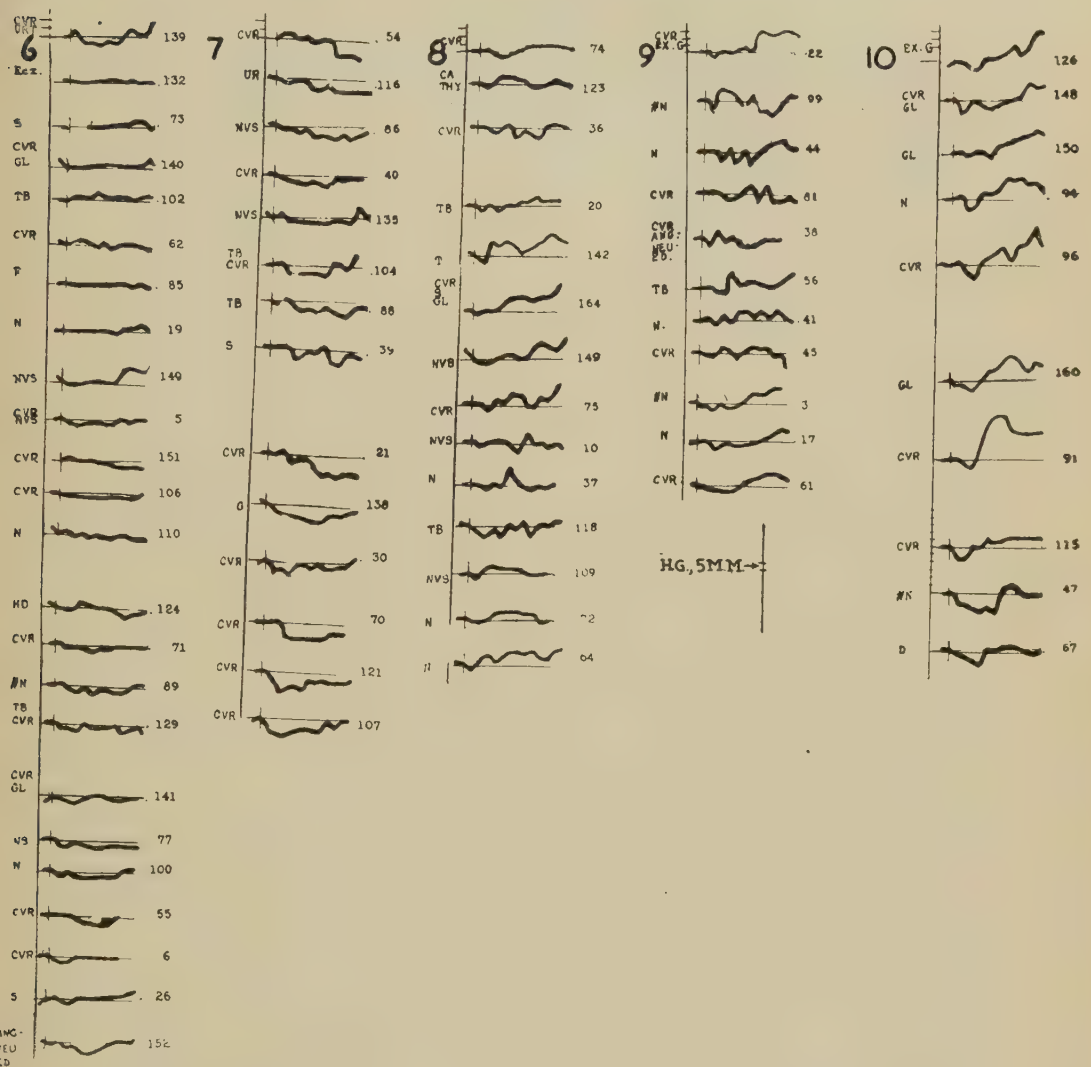

Fig. 2.—Graphic records of systolic blood pressure of "parasympathetic groups."

We now have the outstanding group of contrasting persons and can note that the sympathetic group is characterized by: (1) more permeable skin capillaries; (2) a higher amount of calcium, but a lower potassium calcium ratio; (3) a smaller proportion of albumin in the

TABLE 4.—*Averages for Sympathetic and Parasympathetic Groups*

	Blister Time	Permeability	Inflammatory Index	Calcium	Potassium	Potassium-Calcium Ratio	Sugar	Albumin-Globulin Ratio	Kromayer Time	Basal Metabolism	Skin Resistance	Muscle Reaction	Blood Pressure	Pulse Rate	Reaction to Epinephrine, P. P.	Reaction to Epinephrine, P. P. × P. R.	Carbon Dioxide	Reaction to Ice	Age	Weight-Length Ratio	Cholesterol	Epinephrine, White	Epinephrine, Red	Morphine, White	Morphine, Red	Thyroxin, White	Thyroxin, Red	Caffeine, White	Caffeine, Red
													Sympathetic Group I–V																	
A	8.1	64.6	8.0	10.2	20.0	1.97	72.5	2.01	2.02	9.5	0.533	3.4	123/66	76	18	27	57.2	18.6	45	202	213	19.7	9	11.2	14	12.6	4.8	18.2	2.2
													Parasympathetic Group VI–X																	
	7.6	63.3	8.3	9.9	19.7	2	72.4	2.26	1.79	11	0.4	3.1	122/69	75	7.2	13	57.6	18.4	44.3	218	216	19.2	8.8	11.4	13.6	11.4	4	18.8	2.8
													Sympathetic Group I, II, III																	
B	8.4	65	7.7	10.1	20.5	2.03	74	1.84	2.05	8	0.46	3.8	121/66	77	20	28	57	19.2	42.8	205	213	19.7	9.1	11.2	13.2	12.8	4.2	18.4	2
													Parasympathetic Group VII and X																	
	8.3	61	7.3	9.7	19.6	2.02	72	2.15	1.64	13	0.32	3	133/69	73	7	10	58.1	17.8	49.8	223	213	19.2	8.6	10.4	11.8	11	2.8	20.8	1.4
													Average of First Ten Persons, Group I—Outstanding Sympathetic Cases																	
C	7.7	69.1	9	10.8	18.83	1.74	72.6	2.1	1.72	10.4	0.41	4	123/70	80	21.4	26.7	54.6	23	52	206	219	19.4	9.4	10.6	13.2	12	4	21.2	2.6
													Average of Last Ten Persons, Group VII—Outstanding Parasympathetic Cases																	
	7.7	64.5	8.3	9.64	19.83	2.04	71	2.34	1.95	10.9	0.43	2.3	140/75	80	—1.3	+0.6	57.7	20	50	229	218	20	8.34	10.2	13.2	11.4	3.2	19.2	2.4

serum; (4) a more rapid reaction to the Kromayer lamp; (5) a more sluggish muscle reaction; (6) a lower blood pressure; (7) a lower carbon dioxide combining power; (8) a slightly longer time before reaction to ice occurs; (9) a lower weight-length ratio, and (10) apparently a slight diminution of the size of the morphine and thyroxin wheal in the parasympathetic groups and a somewhat less marked red flare in the reactions to epinephrine, morphine and thyroxin.

It will also be noted that in the more outstanding cases (in sympathetic as well as in the parasympathetic group), the subjects are older than the average, and the pulse rate is higher; in neither group are there absolutely normal persons.

RESULTS OF EXPERIMENTAL WORK

There seems little doubt that the permeability of the capillaries of the skin in the sympathetic group is increased. The ratio for twenty normal persons (38.3 years of age) was found to be 62. The ratio in the groups in which the reaction was sympathetic increased from 64.6 to 65 and finally to 69, as the more marked cases (table 4 A, B, C) were selected. This may have a direct relation to the activity of the thyroid gland, for we find [5] that an increase in permeability is one of the outstanding phenomena of exophthalmic cases, a feature which is promptly influenced by thyroidectomy.[6]

Interest during recent years has centered about the possible relation of the vascular response to epinephrine and the amount of calcium or potassium, or the potassium-calcium ratio. There seems little doubt concerning the general association of calcium with sympathetic effect. Thus injections of calcium chloride increase the blood sugar and make the urine acid; potassium salts have the opposite effect. Calcium increases the pressor effect of epinephrine, while potassium diminishes the effect. Kylin finds that in patients with the lower potassium-calcium quotients, the pressor effect of epinephrine is more marked. With quotients over two, almost every patient examined gave a vagotonic reaction. The literature is reviewed both by Kylin and by Zondek, so that we shall not discuss it at this time.[7]

In the examinations that we have recorded, it is first of all apparent that the entire sympathetic group has a somewhat higher calcium level,

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5. Petersen, W. F.: Permeability of Skin Capillaries in Various Clinical Conditions, Arch. Int. Med. **39**:19 (Jan.) 1927.

6. Article V. The Patient with Exophthalmos and the Nervous Patient, p. 135.

7. Our calcium values for normal subjects are 9.7; potassium, 20.3; the potassium-calcium ratio, 2.1.

the difference between the sympathetic and parasympathetic groups increasing as the more marked cases are selected as shown in table 4:

(*a*) Sympathetic	10.2		
Parasympathetic	9.9	Difference	0.3
(*b*) Sympathetic	10.1		
Parasympathetic	9.7	Difference	0.4
(*c*) Sympathetic	10.8		
Parasympathetic	9.6	Difference	1.2

The corresponding potassium averages and the potassium-calcium ratios are also shown in table 4:

	Potassium	Potassium-Calcium Ratio
(*a*) Sympathetic	20.	1.97
Parasympathetic	19.7	2.
(*b*) Sympathetic	20.5	2.03
Parasympathetic	19.6	2.02
(*c*) Sympathetic	18.8	1.74
Parasympathetic	19.8	2.04

Only in the extreme cases of the "sympathetic" type is there an association of a low potassium-calcium ratio with the sympathetic effect, and in the individual cases there are many conflicting results. This can also be noted in the calcium, potassium and the potassium-calcium ratio for the first three groups in table 3, all of which are strongly sympathetic in reaction. Here the first group (immediate and persistent systolic rise) has a ratio of 1.8; the second group (immediate rise, followed by a fall) a ratio of 2.08, while the third group (slow but continuous rise) has a ratio of 2.22. It would be attractive to postulate that these differences in types of reaction are associated with the differences in the ionic balance, but we should be hesitant in drawing such a conclusion for the following reasons:

The calcium (and potassium) of the serum may reach an identical level under diverse physiologic states of the tissue. There may be a hypercalcemia when calcium is leaving the tissues and increasing in the serum. On the other hand, a hypercalcemia may exist when there is a current in the opposite direction, when calcium excess is being offered the body, and when both the serum and the tissues may consequently be saturated. Under such conditions the reactions of the tissue cells may be diametrically opposite, but the calcium level is the same in both instances. Similar conditions may hold for the potassium level. We have discussed the constant shifting of the calcium and potassium values as observed in previous experimental infections.[8] We must further

8. Petersen, W. F.; Müller, E. F., and Milles, G.: Ztschr. f. d. ges. exper. Med. **60**:336, 1928.

keep in mind that the ionic effect of the calcium may be quite different from that indicated by the total calcium concentration.

It is curious that there is practically no difference in the levels of the sugar content of the respective groups. We might anticipate that the sugar level of the sympathetic series would be higher. This in itself is, we believe, additional proof that the concept of a uniform sympathetic orientation of the individual does not exist. These patients may have a greater response of their vascular musculature, but the hepatic sugar mechanism has not been altered.

There is evident throughout a lesser amount of globulin in the parasympathetic series. Table 4 shows the following $\frac{\text{albumin}}{\text{globulin}}$ ratio in the three series:

(*a*)	Sympathetic	2.01
	Parasympathetic	2.26
(*b*)	Sympathetic	1.84
	Parasympathetic	2.15
(*c*)	Sympathetic	2.1
	Parasympathetic	2.34

The normal ratio is around 2.22.

The averages for the appearance time of the erythema following irradiation by the Kromayer lamp are conflicting. The averages for the larger groupings, 4 A and B, indicate that the sympathetic groups are somewhat less responsive, the figures being:

(*a*)	Sympathetic	2 hours
	Parasympathetic	1.8 hours
(*b*)	Sympathetic	2.05 hours
	Parasympathetic	1.64 hours

When the most marked groups are taken into consideration, the figures are:

(*c*)	Sympathetic	1.6 hours
	Parasympathetic	1.7 hours

indicating merely that the response is in general more rapid in both groups than in the normal person.

Practically no differences exist in the basal metabolic rates for the two groups.

The sympathetic group has in general a higher skin resistance (electrical), but when the most marked group (C) is examined, this difference is not found.

A distinct difference seems to make its appearance in the electrical reactivity of the muscles. This is apparent if one compares the normal

reaction of the muscles—3.7 milliamperes (cathodal closing contraction) to the group averages as shown in table 4:

(*a*)	Sympathetic	3.4 ma.
	Parasympathetic	3.1 ma.
(*b*)	Sympathetic	3.8 ma.
	Parasympathetic	3 ma.
(*c*)	Sympathetic	4 ma.
	Parasympathetic	2.3 ma.

As the parasympathetic group is in general inclined toward alkalosis, the increased muscular irritability evident in the group is in accord with the difference in carbon dioxide combining power.

The blood pressure, as might be anticipated from the known effect of epinephrine on the average hypertonic case, shows a distinct increase for the parasympathetic groups, as shown in table 4:

(*a*)	Sympathetic	123/66
	Parasympathetic	122/69
(*b*)	Sympathetic	121/66
	Parasympathetic	133/69
(*c*)	Sympathetic	123/70
	Parasympathetic	140/75

The pulse rate increases in the final group, in which the most abnormal persons are included. There is no appreciable difference between the sympathetic and parasympathetic groups.

The most marked (C) group would indicate a lower carbon dioxide combining power for the sympathetic group. This is indicated in group (B) as well, while the figures for the larger series (A) reveal no differences. It is generally assumed that the sympathetic status involves acidosis.

The reactivity of the capillaries to ice seems somewhat lessened in the persons in the sympathetic group. While the response of those in the large group (A) is alike, the (B) grouping indicates a difference of 1.4 seconds, and in the (C) grouping this is increased to three seconds. The general slowing up of the reaction from A to C is probably associated with the advancing age, which increases from an average of 45 to 51 years.

The difference between the two groups apparent in the weight-length ratio begins in the A group and progresses, the differences being 0.16, 0.18 and 0.23 in the three groups. This difference seems to be quite conclusive.

It is generally assumed [9] that cholesterol differences are of some importance in constitutional differentiation. Our figures fail to reveal any striking changes in the groups examined.

9. Mjassnikow: Ztschr. f. klin. Med. **105**:228, 1927.

The individual reactions of the various pharmacologic agents used for the skin reactions show considerable latitude, particularly in the case of the red flare that appears in response to thyroxin and caffeine; so the results must be interpreted with considerable caution.

COMMENT AND SUMMARY

If we now seek to interpret our observations, we must consider them in terms of the normal and perhaps compare them to observations made

TABLE 5.—*Results for Normal Persons and for Sympathetic and Parasympathetic Cases and Cases of Exophthalmic Goiter*

	Normal Persons	Parasympathetics Table 4 C	Sympathetics Table 4 C	Exophthalmic Goiter
Number in group	20	10	10	12
Blister time	6.8	7.7	7.7	5.4
Permeability	62	64.5	69	72
Inflammatory index	9.3	8.3	9	13.3
Calcium	9.7	9.64	10.8	10.5
Potassium	20.3	19.83	18.83	21.1
Potassium-calcium ratio	2.1	2.04	1.74	2.03
Sugar	72.8	71	72.6	88
Albumin-globulin ratio	2.22	2.34	2.1	1.79
Kromayer time (minutes)	110	117	103	103
Basal metabolism	+5	10.9	10.4	48
Skin resistance	0.33	0.43	0.41	0.23
Muscle reaction	3.7	2.3	4	2.8
Carbon dioxide combining power	57.6	57.7	54.6	54.2
Blood pressure	116/70	140/75	123/70	140/70
Pulse pressure	46	65	53	70
Pulse rate	68	80	80	102
Reaction to epinephrine				
P. P. in per cent	19.6	—1.3	21.4	19
P. P. × P. R. in per cent	28.6	0.6	26.7	33.7
Reaction to ice	14.5	20	23	10
Weight-length ratio	224	229	206	201
Cholesterol	222	218	209	203
Epinephrine wheat (mm.)	21	20	19.4	16
Epinephrine flare (mm.)	9.36	8.34	9.4	10.6
Morphine wheat (mm.)	11.7	10.2	10.6	11.4
Morphine flare (mm.)	16.3	13.2	13.2	11.6
Thyroxin wheal (mm.)	11.6	11.4	12	10.4
Thyroxin flare (mm.)	5.45	3.2	4	4.6
Caffeine wheal (mm.)	17.9	19.2	21	15.2
Caffeine flare (mm.)	3	2.4	2.6	1
Age	40.2	50	52	39

in a disease condition in which sympathetic overbalance has been frequently suggested, mainly that of exophthalmic goiter. We have tabulated the most important results for normal persons, for our outstandingly contrasting sympathetic and parasympathetic cases, and for cases of exophthalmic goiter.[10]

10. Exophthalmic goiter by no means represents a purely sympathetic overbalance; the autonomic manifestations are obviously mixed in character (Eason, J.: Exophthalmic Goiter, Edinburgh, Oliver & Boyd, 1927).

Thus it becomes apparent that the sympathetic group approaches the exophthalmic goiter in permeability, in high calcium concentration, in shortening of the Kromayer time, in relative acidity, in response to epinephrine, in weight-length ratio and in relatively low cholesterol content. This group approaches the parasympathetic group, on the other hand, in the electrical response, as well as in the higher systolic blood pressure.

Chart 3 illustrates the relative skin reactions noted in table 4.

An analysis of the reaction to epinephrine has been made on 100 so-called normal persons, as well as on about fifty patients. In contrast-

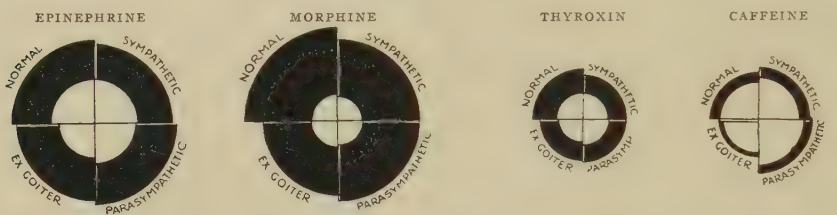

Fig. 3.—Average wheal (white) and flare (black) following intracutaneous injection of epinephrine, morphine, thyroxin and caffeine into normal persons, patients with exophthalmic goiter and the sympathetic and parasympathetic "groups" (4 C).

ing the outstanding sympathicotonic cases with the outstanding vagotonic cases, the average indicate that the sympathicotonic group differs in that the members of the group have more permeable skin capillaries, a lower potassium-calcium ratio, more globulin, a lower carbon dioxide combining power and a lessened muscular electrical reactivity. The persons weigh less and have a lower blood pressure.

Comparative data are also presented for twenty normal persons, twelve patients with exophthalmic goiter and the most marked sympathicotonic and vagotonic types.

V. THE PATIENT WITH EXOPHTHALMOS AND THE NERVOUS PATIENT*

In a previous communication, we called attention to the fact that the blister time of the patient with exophthalmos is considerably shortened, and that the permeability of the capillaries of the skin, as measured by the relative amount of protein in the blister, is markedly increased.[1]

It is a well known clinical observation that the skin of the patient with exophthalmos is thinner and more transparent than that of a normal person, and vasomotor lability is plainly evidenced by the rapid flushing and pallor. The arterioles, as well as the capillaries, are dilated. The functional status of the skin is one of exaggerated activity involving both the radiation of heat and evaporation. It has recently been shown that the secretory activity of the sweat glands of the skin is controlled by a skin plexus largely independent and locally autonomic, although the sympathetic nerves are commonly regarded as the nerves having to do with secretory functions. We have used the term parasympathetic status to designate this condition of activity of the skin for reasons discussed elsewhere.[2]

Among our group of patients there have been twelve with typical exophthalmos, as well as one patient with hyperthyroidism associated with carcinoma of the thyroid, and one patient who was being treated with thyroid extract (basal metabolic rate + 31) following a thyroidectomy. In six of the patients, we were able to carry out a complete reexamination several months after the thyroidectomy.

CLINICAL HISTORIES OF "SYMPATHETICOTONIC" PATIENTS AND PATIENTS WITH EXOPHTHALMOS

CASE 9.—A white man, aged 36, had become ill with palpitation and tachycardia fourteen months previous to the examination. He had lost 10 pounds (4.5 Kg.). Eight months later, he had a similar attack. Occasionally, he had night sweats. He had a rather coarse tremor. On exertion he showed slight dyspnea. At the time of examination, he had the papular and pustular lesions of acne. The conjunctivae were slightly injected. A few cervical glands were palpated below the angle of the jaw, and there was a light contraction of the superclavicular fossa. The blood pressure was 132 systolic and 86 diastolic. The basal metabolic rate on December 24 was + 34, and on December 28 was + 49. There was no exophthalmos. In this case, the disease was mild.

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* In collaboration with Dr. Lindon Seed of the Department of Surgery, University of Illinois College of Medicine.

1. Petersen, W. F.: Permeability of Skin Capillaries in Various Clinical Conditions, Arch. Int. Med. **39**:19 (Jan.) 1927.

2. Petersen, W. F., and Müller, E. F.: Splanchnoperipheral Balance During Chill and Fever, Arch. Int. Med. **40**:575 (Nov.) 1927.

CASE 11.—A white man, aged 46, had been nervous, with tachycardia and sweating for the past eight months. He had a tremor, and was dyspneic. He had been irritable for about a year. There was no exophthalmos. The pulse rate was 80; the blood pressure was 120 systolic and 60 diastolic. His normal weight was 176 pounds (79.8 Kg.); at this time it was 136 pounds (61.7 Kg.). The neck showed a soft fulness in the region of the thyroid gland. The presence of exophthalmos was questionable. The heart seemed to be heaving somewhat, but no murmurs were apparent. The x-ray diagnosis was myocarditis. The urine was normal. The basal metabolic rate was + 42. In this case, the disease was mild.

CASE 16.—A white man, aged 33, had been sick for ten months. His illness had begun with nervousness, tremor, fatigue, palpitation and occasional nausea. At the time of observation, the patient was feeling better, but still had some dyspnea. His normal weight was 152 pounds (68.9 Kg.); at the time of the examination it was 124 pounds (56.2 Kg.). The pulse rate was 90; the blood pressure was 133 systolic and 70 diastolic. He showed no exophthalmos. The thyroid gland was diffusely enlarged. A systolic murmur was heard over the aortic valve. A trace of albumin was found in the urine. The basal metabolic rate was + 20. Clinically, the case was debatable. The results of the laboratory examinations were also doubtful. The albumin/globulin ratio was high (5.6), and there was a possibility of tuberculous activity in the right apex that would account for some of the symptoms.

CASE 22.—A white man, aged 58, had become ill, three months previous to examination, with tremor, palpitation, nervousness, loss of strength and excessive perspiration. The blood pressure was 134 systolic and 64 diastolic. There was no exophthalmos. A moderately large diffuse thyroid gland of firm consistency was noted. The urine was normal. The basal metabolic rate was + 44. The pulse rate was 100. The x-ray diagnosis was: heart, large; mitral lesion (?). In this case, the disease was mild.

CASE 119.—A white woman, aged 43, had felt a marked general weakness for two years; she perspired easily. During this time she had lost 20 pounds (9 Kg.), despite a good appetite. She had a slight enlargement of the thyroid gland. At the time of the first examination, the basal metabolic rate was + 13 and the pulse rate 82. In addition to the endocrine disturbance, she gave some evidence of having arthritis deformans (x-ray diagnosis). No exophthalmos was observed. In this case, the disease was mild.

CASE 31.—A white woman, aged 42, began to have a swelling of the thyroid two years previous to examination. At the times of menstruation she had nausea and vomiting with increased hemorrhage. The illness had commenced with nervousness, after the birth of her sixth child, and had been particularly accentuated during her seventh pregnancy. She had diarrhea occasionally, and tremor. She had lost 44 pounds (20 Kg.) in the last ten months. Her normal weight was 175. Her weight at this time was 138 pounds (62.6 Kg.). She had a nervous breakdown three weeks before examination. The blood pressure was 115 systolic and 75 diastolic. No exophthalmos was observed. The thyroid gland was soft and the right lobe and the isthmus were particularly enlarged. The urine was normal. The basal metabolic rate on January 27 was + 73, and on January 31, + 44. In this case, the condition was moderately severe.

CASE 51.—A white woman, aged 58, had become ill four months prior to examination, with a loss of 50 pounds (22.7 Kg.) in weight, nervousness, the sensation of warmth and palpitations. She had vomited occasionally, and had had diarrhea. There was slight exophthalmos and the thyroid gland was moderately enlarged. A tremor was present. The urine was negative. The basal matabolic rate on

February 19 was + 67. The blood showed a sugar value of 120 mg., a nonprotein nitrogen value of 32 mg., and a urea value of 17 mg. The Wassermann reaction was negative. In this case, the disease was moderately severe.

CASE 58.—A white woman, aged 39, began to have a swelling of the thyroid gland four years prior to examination. Her illness dated back one year to a time when she grew irritable. She perspired freely and had a tremor. Exophthalmos was marked. There had been little loss of weight and the appetite was good. The goiter felt firm. The urine was normal. The basal metabolic rate was + 94 on March 23 and + 80 on March 24. The Wassermann reaction was negative. The blood sugar was 100 mg. The nonprotein nitrogen was 32 mg. In this case, the condition was moderately severe.

CASE 159.—A white man, aged 53, became ill in November, 1925; he felt weak, and lost 45 pounds (20.4 Kg.). After that he had periods of nervousness. Exophthalmos and tremor were noted (July, 1927) in the dispensary and a myocarditis was suspected (pulse rate, 96; blood pressure, 124 systolic and 60 diastolic; dyspnea, and diastolic murmur at the base). On August 2, the basal metabolic rate was + 42; it was the same in October, 1927, when we made our examination. At this time the patient was improving.

CASE 125.—A white woman, aged 29, began to be ill, eleven months prior to examination, with palpitation, weakness, loss of 57 pounds (25.9 Kg.) in weight, nervousness and excessive perspiration. The illness in question began with nausea and vomiting. Exophthalmos was present. There was a diffuse, soft enlargement of the thyroid gland. The urine was normal. The basal metabolic rate on July 2 was + 58; on July 23, + 85, and on July 27, + 59. The blood pressure was 170 systolic and 85 diastolic. The pulse rate was 140. This was a severe case.

CASE 126.—A white man, aged 21, began to be ill, four months prior to examination, with nervousness, tremor and loss of strength. His normal weight was 157 pounds (72.1 Kg.) and he had lost about 20 pounds (9 Kg.). He felt weak and perspired freely. The blood pressure was 142 systolic and 60 diastolic; the pulse rate was 112. There was moderate exophthalmos and diffuse general enlargement of the thyroid. The urine was normal. The basal metabolic rate on July 2, 1927, was + 25. The sugar was 83 mg.; the nonprotein nitrogen, 37 mg. This was a severe case.

CASE 131.—A white woman, aged 59, began to be ill, sixteen months prior to examination, with nervousness. She had a nervous breakdown one year before examination, together with palpitation and the feeling of warmth, occasional vomiting and diarrhea. Her loss in weight had been 80 pounds (36.3 Kg.), i. e., from 204 to 118 pounds (92.5 to 53.5 Kg.). There was a moderate enlargement of the thyroid gland and slight exophthalmos. The urine showed a trace of albumin. The basal metabolic rate on July 15 was + 88. In this case, the disease was severe.

CASE 57.—A white woman, aged 38, commenced being ill with palpitation six months before examination. For three months prior to examination she had been nervous and weak, had perspired readily and had lost 40 pounds (18.1 Kg.). She had been nauseated for about two months. Exophthalmos was not marked. The urine was normal. The basal metabolic rate was + 150. A goiter had been removed three months previous to examination. About Jan. 1, 1927, the patient began to feel weak and noticed lacrimation, impaired vision and slight swelling of the face. The patient returned on March 7 with some evidence of myxedema. She was given a course of treatment with thyroid extract. Our examination was made on February 22; at this time, the effect of the thyroid extract was apparent in a basal metabolic rate of + 31.

TABLE 1.—*Results of Correlative Examinations*

	Individual Number	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Wassermann Reaction	Kromayer Light Erythema Time, Hours	Basal Metabolic Rate	Skin Resistance	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure: Systolic	Blood Pressure: Diastolic	Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure × Pulse Rate, %	CO_2 Combining Power	Endothelial Reaction
Mild	9	5.5	71	13	11.5	23.5	2.04	88	1.7	..	2	+49	0.75	2.2	..	140	70	96	+28 + 6	+46	61.5	+
	11	5	70	14	10.9	24.1	2.21	82	3	..	3	+42	0.14	5.5	..	124	74	108	+ 9	58.1	....	..
	16	5	80	16	11.4	21.6	1.9	75	5.6	..	2.25	20.8	0.11	1.9	+	150	68	88	22	35	55.3	..
	22	6	73	12	12.1	18.2	1.5	91	...	..	1.25	44	0.17	3	..	144	74	92	+31	+44	52	+
	119	6.45	58	8.5	9	18.7	2.1	75	1.7	..	1.25	34	0.08	3	..	142	82	98	+13	+24	55.4	..
Mod. severe	31	5.5	70	12.7	9.5	....	....	..	0.28	..	....	+73	....	...	..	115	75	114	....	....	49.2	..
	51	5	77	14	10	25.8	2.58	91	5.4	..	Did not appear	+67	0.13	5	..	124	50	104	25	35	55	..
	58	5	75	15	12	25.9	2.5	120	1.2	..	1.10	+43	0.10	...	..	144	60	127	+ 2	+ 5	52.9	..
	159	5	69	14	8.23	17.9	2.17	71	No globulin	..	1.18	+46	0.22	...	Trace	132	68	80	+17	+30	54.8	..
Severe	125	6	74	12	11.5	....	....	81	0.66	..	1.5	59	0.48	1.5	..	170	85	140	....	....	55.5	+
	126	6	..	..	9	18	2	77	2.3	..	?	105	0.20	0.8	?	148	66	90	20	23	60.6	..
	131	5	77	15.4	9.6	18	1.87	113	1	..	2	+88	0.21	...	+	...	..	...	....	....	44.6	..
	57	7.75	80	10.3	....	24.7	....	92	2.3	..	2.15	+31	0.55	...	..	94	61	78	+34	+50	60.2	..
	123	9.25	74	8	9.2	20	2.17	81	2.4	..	?	+48	....	2.2	+	165	100	81	— 3	+ 5	52.4	+
	Av.	5.89	72.9	12.68	10.3	21.4	2.09	79.7	2.6	..	1.77	+48	0.25	2.79	..	146	72	100	+19	+33	54.5	..

TABLE 2.—*Comparison of the Averages of the Reactions of a Group of Patients Men, a Group of "Sympatheticotonic" Persons*

Group	Blister Time, Hours	Permeability of Capillaries	Inflammatory Index	Kromayer Light Erythema Time, Min.	Ice Reaction Time, Seconds	Skin Resistance	Intracutaneous Reactions to Pharmacologic Substances: Epinephrine Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
20 normal men	6.8	62	9.3	110	14.5	0.33	21	9.36	11.7	16.3	11.6	5.45	17.9	3
6 patients with exophthalmos, before operation	5.3	75	14	110	19	0.13	21.9	8.4	10.7	13	10	7.6	13.6	0
after operation	7.4	62	10.7	70	9	0.23	20	12.5	13.5	7	17	1.3	16	6.5
10 "sympatheticotonic" persons	7.7	69.1	9	103	23	0.41	19.4	9.4	10.6	13.2	12	4	21.2	2.6
12 "nervous" patients	7.5	69.1	9.2	112	20.4	0.79	18.3	10	11.6	14.6	14	6.8	18.6	3.8

of Patients with Exophthalmic Goiter

Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)	Diagnosis
Asthenic	.....	+	Granulation	..	27	200	...	....	....	....	....	....	...	....	...	
Asthenic	Healed	0	Normal	..	46	195	...	....	....	....	....	....	...	....	...	Myocarditis (x-ray diagnosis)
Asthenic	?	+	Normal	7	33	195	...	....	....	7.2	18	....	...	....	...	Possibility of active tuberculosis of right apex (healed tuberculosis) (x-ray)
Nervous	Healed	+	+	5	38	233	...	26.4	10.2	15	10	5	1	7	0	Heart large; mitral lesion (x-ray)
Nervous	.....	..	Normal	10	43	266	330	24	5	12	11.2	12	7	17.4	5.6	Arthritis deformans (x-ray)
Nervous	.....	0	Normal	.. (40)	42	200	...	21.6	7	9	13.6	7.2	...	7.4	3.6	
Sthenic	.....	..	Normal	5	58	195	...	19.2	6.2	11	13.4	9.2	4.8	9	...	
Asthenic	.....	..	Normal	25	29	188	...	19.6	10.4	9.8	13.8	11.2	6.8	12	...	Myocarditis (x-ray) ?
Sthenic	.....	..	.....	7	53	196	158	25	9	6.4	3.5	12	0	15	0	
Sthenic	Healed	+	Normal	18	29	...	190	22.4	7	10.4	9	15.2	17	26.4	...	Myocarditis (right lung, increased fibrosis) (x-ray)
Sthenic	.....	..	Normal	5	21	174	190	19.6	7	....	....	12	...	32.4	...	
Sthenic	.....	+	Normal	7	59	177	147	16.8	6.2	12	8.8	10.4	6.2	10	...	
Sthenic	.....	+	Normal	6	39	221	...	18.4	7.4	12.4	15.4	12.2	14	20.2	5	Hyperthyroidism; on extract after operation
Sthenic	.....	+	Normal	8	68	263	171	20	6.8	11.2	10.2	10	11.2	19.2	...	Hyperthyroidism with carcinoma of the thyroid gland; aortitis
.....	.....	..	.....	8.6	42	208	197.6	21.2	7.5	10.6	11.5	10.6	6.4	16	2.8	

with Exophthalmos with the Averages of the Reactions of a Group of Normal and a Group of "Nervous" Persons

Blood Chemistry					Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure × Pulse Rate, %	Blood Pressure		Pulse Rate	Basal Metabolic Rate	Weight/Length Ratio	Age
Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	CO_2 Combining Power	Sugar, Mg.			Systolic	Diastolic				
9.7	20.3	2.1	57.6	72.8	+19.6	+28.6	116	70	68	+ 5	224	40.2
11.3	23.1	2.04	54.1	91	+17	+25	142	70	110	+46	200	39
9	18.5	2.04	63	71	+ 9	+17	123	70	85	+ 7.6	240	39
10.8	18.83	1.74	54.6	72.6	+21.4	+26.7	123	70	80	+10.4	206	52
10.8	18.8	1.74	57.8	76	+10.5	+22.5	120	64	80	+ 8.5	198	33.6

Case 123.—A white woman, aged 68, had had a carcinoma of the uterus fifteen years previously, which was removed. Four years prior to the examination, she had had a malignant tumor of the thyroid gland, which she subsequently had had removed three times. At the time of the examination, she suffered from dyspnea caused by the growth, considerable loss of weight during recent months and some evidence of hyperthyroidism. The roentgen examination of the chest revealed a large heart and aortitis. The blood pressure was 182 systolic and 100 diastolic. The tumor was regarded as inoperable. No exophthalmos was noted. The symptoms in this case were mild.

In table 1, we have grouped the results of the various examinations carried out in these cases, the first five cases being mild, the next four moderately severe and the last group severe.

For purposes of comparison with the normal, we present in table 2 the averages for twenty normal persons, six patients with exophthalmos before and after operation, ten "sympatheticotonic" [3] patients and twelve "nervous" persons.

In table 3, the individual reactions of six patients with exophthalmos before and after operation are shown.

COMMENT

Blister Time.—As previously shown,[2] the cantharides blister time is markedly shortened in the patients with exophthalmos. We presume that this is, in general, due to the increased parasympathetic status of the periphery. Following removal of the thyroid gland, the blister time is lengthened. Seemingly, the blister time is not necessarily related to the basal metabolic rate; for in case 123 (carcinoma with hyperthyroidism; basal metabolic rate + 48), the blister time was not shortened, nor was it in case 57 (therapeutic hyperthyroidism following insufficiency due to thyroidectomy; basal metabolic rate + 31). On the other hand, in case 22, thyroidectomy was followed by a considerable shortening of the blister time, despite the lowering of the basal metabolic rate to + 3. The patient in this case gave other evidence of continued autonomic disturbance.

Permeability of Capillaries.—The relative amount of protein present in the blister is high in the case of exophthalmic goiter. We regard this as evidence of increased capillary permeability.[4] It will be observed that both the "sympatheticotonic" and the "nervous group" approach the patients with exophthalmos in this respect. Following thyroidectomy, permeability is diminished in all cases. Both the hyperthyroidism associated with carcinoma and that following treatment with thyroid

3. The Relation of the Reaction to Epinephrine to the Potassium/Calcium Ratio and to Other Ratios, p. 121.

4. Petersen, W. F., and Willis, D. A.: Capillary Permeability and Inflammatory Index of Skin in Normal Person as Determined by Blister, Arch. Int. Med. **38**:663 (Nov.) 1926.

extract are associated with high permeability. The increase in permeability seems directly related to thyroid activity in some way, but not necessarily with the factor that is responsible for the increase in basal metabolic rate. In case 16 (in which the basal metabolic rate did not change following thyroidectomy) the capillary permeability diminished. On the other hand, in patient 119 (arthritis deformans, adenoma of the thyroid; basal metabolic rate +34) the permeability was low, but the patient had some of the symptoms of hyperthyroidism.

Calcium.—Contrary to the observation of Kylin [5] and Leicher,[6] we have, in general, found an increase in the calcium of the serum; the average for our twelve cases is 10.4, and for the six cases studied before and after operation the respective values are 11.3 and 9. Our results agree with those of Jacobsohn and Rothschild.[7] Herzfeld and Neuburger [8] reported conflicting results. Whether or not the high calcium level is partly responsible for the sympatheticotonic effects we cannot state. It has been previously demonstrated that calcium is lost from the body during treatment with thyroid (Bolaffio, Tedesco and Falta [9]).

Potassium and the K/Ca Ratio.—As the potassium is increased proportionally to increase in calcium, the K/Ca ratio remains approximately at 2. After thyroidectomy, the potassium level drops with the calcium level and the ratio remains constant. At the operation, both upper parathyroids were removed, with approximately two thirds of the thyroid tissue.

Albumin/Globulin Ratio.—In severe cases there is a considerable increase in serum globulin. We doubt whether this is a specific effect, because it occurs so frequently in severe intoxications. Following thyroidectomy, the albumin again increases. In sympatheticotonic persons the globulin shows a slight increase.[3]

Neither the change in the calcium and the potassium levels nor the change in the albumin/globulin ratio is due to changes in the concentration of the serum, for we find that the serum proteins are, if anything, more concentrated after the thyroidectomy. Similar changes were reported by Frowein.[10]

Kromayer Light Erythema Time.—In patients with exophthalmos, the time of the appearance of the erythema following application of the Kromayer light is somewhat shortened following thyroidectomy. This

5. Kylin, E.: Acta med. Scandinav., 1928, suppl. 19, p. 1.
6. Leicher, H.: Deutsches Arch. f. klin. Med. **141**:85, 1923.
7. Jacobsohn, M., and Rothschild, F.: Ztschr. f. klin. Med. **105**:417, 1927.
8. Herzfeld, E., and Neuburger, J.: München. med. Wchnschr. **71**:1324, 1924.
9. Bolaffio, Tedesco and Falta: Wien. klin. Wchnschr. **22**:1059, 1919.
10. Frowein, W.: Ztschr. f. d. ges. exper. Med. **24**:162, 1921.

is even markedly apparent in one patient (no. 51) in whom no erythema appeared before operation, but after operation it appeared in 100 minutes.

Reaction to Ice.—The shortness of the Kromayer light erythema time is paralleled by the rapidity of the appearance of erythema following the local application of ice. Possibly, the lessening of the peripheral sympathetic tonus accounts for the more rapid reaction, although the so-called "parasympathetic" person shows little difference from the "sympathetic" person in this reaction.[3]

Resistance of Skin to Electric Current.—A rather striking difference exists in the resistance of the skin to electric current. This is somewhat reduced in exophthalmic goiter (a similar observation was made by Richter[11]), but after operation it returns to normal. Whether this response is modified by the enhanced sweating of the patient with exophthalmos we leave undetermined. Lueg and Grassheim[12] studied the electric condensation values of the skin. These, too, are altered in exophthalmic goiter.

CO_2 Combining Power.—The CO_2 combining power is slightly lowered before, and returns to a supernormal level after thyroidectomy. This is in agreement with the determinations of Hollo and Weiss,[13] Morros[14] and Walinski and Herzfeld.[15]

Intracutaneous Reactions to Pharmacologic Substances.—The reactions of the skin to pharmacologic substances are of some interest. As compared with the reaction of a normal person, the wheal due to epinephrine hydrochloride in a patient with exophthalmos is somewhat increased and the flare lessened; the wheal and the flare due to morphine are diminished; the wheal due to thyroxin is diminished, but the flare is increased; the wheal and the flare due to caffein are diminished. After operation there is a distinct reversal in the reaction to epinephrine in that the wheal is again diminished, but the flare increased. In the reaction to morphine, the wheal is again increased, but the flare is decidedly contracted, the same being true in the reaction to thyroxin. That these changes are associated with hyperthyroidism and not necessarily with the associated autonomic changes which are by some assumed to underly the pathologic alterations seems indicated from the reactions

11. Richter, C. P.: Electrical Skin Resistance; Diurnal and Daily Variations in Psychopathic and in Normal Persons, Arch. Neurol. & Psychiat. **19**:488 (March) 1928.

12. Lueg, W., and Grassheim, K.: Klin. Wchnschr. **7**:647, 1928.

13. Hollo, I., and Weiss, S.: Klin. Wchnschr. **3**:163, 1924.

14. Morros, J. S.: Arch. Endocrinol. **4**:279, 1926.

15. Walinski, F., and Herzfeld, E.: München. med. Wchnschr. **73**:2153, 1926.

TABLE 3.—*The Results of Correlative Studies of Six Patients with Exophthalmos Before and After Thyroidectomy* *

Case	11	16	22	51	58	125	Averages
Blister Time, Hours							
Before operation	5	5	6	5	5	6	5.3
After operation	7.5	5.5	2.5	10	6.5	12	7.4
Permeability of Capillaries, per Cent							
Before operation	70	80	73	77	75	74	75
After operation	66	66	66	60	58	60	62
Inflammatory Index							
Before operation	14	16	12	14	15	12	14
After operation	8.5	12	25	6	8	5	10.7
Kromayer Light Erythema Time, Min.							
Before operation	180	135	75	Did not appear	75	90	110
After operation	58	60	66	100	90	66	70
Reaction to Ice, Seconds							
Before operation	?	7	5	40	25	18	19
After operation	25	7	10	10	9	10	9
Skin Resistance							
Before operation	0.14	0.11	0.17	0.13	0.1	0.48	0.13
After operation	0.23	0.5	0.11	0.11	0.18	4.4	0.23
Endothelial Reaction							
Before operation	—	—	—	—	—	+	Unchanged
After operation	—	—	—	—	—	+	—
Epinephrine, Wheal, Mm.							
Before operation	....	....	26.4	19.2	19.6	22.2	21.9
After operation	15.2	17	18	20	18	23	20
Epinephrine, Flare, Mm.							
Before operation	....	...	10.2	6.2	10.4	7	8.4
After operation	18	12.5	13	12.5	15	10	12.5
Morphine, Wheal, Mm.							
Before operation	....	7.2	15	11	9.8	10.4	10.7
After operation	13	12	11	17.5	12	15	13.5
Morphine, Flare, Mm.							
Before operation	....	18	10	13.4	13.8	9	13
After operation	14.75	7.7	10.15	8.75	0	10.7	7.5
Thyroxin, Wheal. Mm.							
Before operation	....	....	5	9.2	11.2	15.2	10
After operation	....	18	9	22	....	24	17
Thyroxin, Flare, Mm.							
Before operation	....	....	1	4.8	6.8	17	7.6
After operation	....	0	0	0	....	4.5	1.3
Caffein, Wheal, Mm.							
Before operation	....	....	7	9	12	26.4	13.6
After operation	9	21	9	24	16	25	16
Caffein, Flare, Mm.							
Before operation	....	....	0	0	0	0	0
After operation	0	0	0	10.5	0	2.5	6.5
Serum Protein, per Cent							
Before operation	7.2	7.2	7.76	7.85	8.28	9.13	7.92
After operation	8.7	6.12	8.7	7.41	8.38	9.76	8.18
Calcium, Mg.							
Before operation	10.9	11.4	12.1	10	12	11.5	11.3
After operation	8.54	9.65	9.81	?	7.76	9.6	9.07
Potassium, Mg.							
Before operation	24.1	21.6	18.2	25.8	25.9	?	23.1
After operation	17.75	20.7	20.4	19.24	13.49	19.7	18.5
K / Ca Ratio							
Before operation	2.21	1.7	1.5	2.58	2.15	?	2.04
After operation	2.08	2.14	2.08	?	1.74	2	2.04
CO_2 Combining Power							
Before operation	....	55.3	52	55	52.9	55.5	54.1
After operation	57.5	66.2	74	62.2	50.1	62.6	63
Albumin / Globulin Ratio							
Before operation	3	5.6	?	0.54	1.2	0.66	2.2
After operation	No globulin		7.3	4.5	1.9	2.7	....
Sugar, Mg.							
Before operation	82	81	91	91	120	81	91
After operation	61	67	71	90	71	67	71
Reaction to Epinephrine:							
Increase in Pulse Pressure, per Cent							
Before operation	+0.06	+27	+31	+25	+2	?	+17
After operation	14	10	15	7	0	9	+9
Increase in Pulse Pressure × Pulse Rate, per Cent							
Before operation	9	35	44	35	5	?	25
After operation	23	17	35	16	0	13	17
Pulse Rate							
Before operation	108	88	92	104	127	140	110
After operation	84	72	80	74	90	100	85
Blood Pressure, Systolic/Diastolic							
Before operation	124/74	150/68	144/74	124/50	144/69	170/85	142/70
After operation	118/78	134/70	124/66	105/77	130/72	126/80	123/74
Pulse Pressure							
Before operation	50	82	70	74	75	85	72
After operation	40	64	58	27	58	46	49
Weight/Length Ratio							
Before operation	195	195	233	195	188	...	200
After operation	234	186	288	270	222	210	240
Basal Metabolic Rate							
Before operation	42	20	44	67	43	59	46
After operation	—8	20	3	—12.6	16.5	21	7.6

* The determinations before operation are placed in the upper line and those after operation in the lower line of each bracket.

of the skin in patient 123, which, in general, agree with the observations of the other patients with exophthalmos. This particular patient was suffering from carcinoma of the thyroid gland and not from true exophthalmic goiter, there being presumably no underlying or preceding autonomic disturbance.

PREOPERATIVE AND POSTOPERATIVE REACTIONS

When one examines table 3 showing the reactions before and after thyroidectomy, it becomes apparent that a dissociation of certain of the reactions exists.

In case 16, for instance, thyroidectomy was not followed by clinical improvement. The basal metabolic rate remained unchanged (+ 20), the weight diminished, the patient felt weak and a moderate tremor persisted. It will be noted that the blister time remained practically unaltered, as did the time of the reaction to ice.

The reaction of the skin to Kromayer light, the resistance to electrical current and the reaction to morphine followed the typical courses, the capillary permeability diminished and all the chemical and cardiac reactions returned toward the normal.

In case 22, on the other hand, the basal metabolic rate was lowered, and the weight of the patient increased; nevertheless, some of the reactions of the skin showed a distinct abnormality. Thus, the blister time was short, the resistance of the skin to electric current was diminished, and the reaction to morphine was reversed, the reaction to ice was prolonged and the reaction to the Kromayer light was unaltered. The permeability of the capillaries, however, showed normal diminution. Chemically, the only deviation was an increase in potassium instead of a diminution. Clinically, this patient improved.

It seems obvious that one cannot make merely an augmented secretion from the thyroid responsible for all alterations in these autonomic reactions, because if this were the only factor, all of them should return toward the normal after operation, while, as may be observed, there is sometimes a distinct difference in the reactions—for example, in one case the return of the basal metabolic rate to normal, and in the other a persisting increase in the rate.

If one now examines table 2 and compares the results of the examinations of the normal persons with the results of the examinations of the group with exophthalmos before and after operation, it becomes evident that, despite the restoration of weight, the normal basal metabolic rate and the relief of clinical symptoms, decided alterations of the reactions of the skin are still manifest. Thus, the resistance of the skin to electric current remains low; the ice reaction time and the Kromayer light erythema time are short; the red flare of the reaction to epinephrine is increased, while that of the reaction to

morphine is diminished; the wheal in the reaction to thyroxin is increased while the flare is diminished, and in some cases, the flare in the reaction to caffein seems also increased.

CLINICAL HISTORIES OF THE NERVOUS PATIENTS

In the nervous group, our material consists of four persons from the so-called "normal" series, three medical students and a small number of persons studied in the Research Hospital. We have not sought to examine a large series of neurasthenic persons, but have merely grouped the persons who came under observation in the routine study in whom nervousness played a large rôle in the symptom complex (table 4).

CASE 80.—An electrician, an American, aged 29, had a distinct tremor and felt nervous. The onset had followed an explosion in a mine in 1924. He had had urticaria in 1922. He was a moderate smoker.

It is to be noted that: the capillaries were very permeable; the calcium level was potassium levels were low, as was the K/Ca ratio; the capillaries of the skin showed some granulation; the flares about the sites of the intracutaneous injections of pharmacologic substances were wide; the reaction to ice was delayed and faint; the resistance of the skin to electric current was high; the erythema resulting from the application of the Kromayer light was marked.

CASE 92.—A medical student, Jewish, aged 22, was nervous, sweated easily and had an occasional tremor. He suffered from lassitude and inability to concentrate. He had a bowel movement once or twice a week.

It is to be noted that: the capillaries were very permeable; the calcium level was low, while the K/Ca ratio was high; the reaction to epinephrine was strongly sympatheticotonic; the flares of the reactions to pharmacologic substances were all wide, and the reaction to the Kromayer light was faint.

CASE 135.—A tailor, Jewish, aged 29, felt nervous and weak, and had had some night sweats and some loss of weight (12 pounds [5.4 Kg.] in one year). The basal metabolic rate was + 17. This patient was under observation in the Research Hospital for possible exophthalmic goiter.

It is to be noted that: the capillaries showed increased permeability; the K/Ca ratio (1.8) was somewhat lowered; the globulins were increased; occasional granular casts were observed in the urine; the capillaries of the skin showed evidence of a beginning granulation and beading; the reaction to epinephrine was "vagotonic"; the flares of the pharmacologic skin reactions were diminished, and there were roentgenologic evidences of a probably healed tuberculosis.

Of these three cases, therefore, only the third gave evidences of organic disturbances (granular casts), but in all of them there was high permeability of the capillaries, as well as an alteration of the calcium level or the K/Ca ratio.

In the next four cases, a moderate increase of capillary permeability was shown.

CASE 5.—A housewife, Jewish, aged 48, the wife of patient 6, had vague pains all over the body, and was nervous.

It is to be noted that: the calcium level was high, but the K/Ca ratio was within normal limits; there was a trace of albumin in the urine, and the heart and aorta appeared large on roentgen examination.

CASE 109.—A spinster, American, aged 42, became weak after unilateral ovariectomy fifteen years prior to examination. Following this, she was nervous, had palpitation, perspired excessively and spent much time in bed because of weakness. One sister had hyperthyroidism.

It is to be noted that: the potassium level and the K/Ca ratio were outstandingly low; the basal metabolic rate of + 55 was questionable, the test being unsatisfactory because the patient was extremely nervous; the pulse rate was increased; the CO_2 combining power was low; the blood cholesterol level was high;

TABLE 4.—*The Results of Correlative Exam*

Individual Number	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Sugar, Mg.	Albumin/Globulin Ratio	Wassermann Reaction	Kromayer Light Erythema Time, Hours	Basal Metabolic Rate	Skin Resistance	Muscle Reaction, Ma.	Changes in Urine	Blood Pressure		Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction. Pulse Pressure × Pulse Rate, %
															Systolic	Diastolic			
80	6	91	15.1	8	13.7	1.7	69	2	..	16.5	+13	1.6	3.8	..	116	68	64	+ 7	+12
92	9	83	8	8.4	19.5	2.32	67	2.8	..	1.5	— 0.8	0.57	2	..	110	60	72	+46	+70
135	6	84	14	10.8	19.6	1.81	75	1.2	..	1.25	+17.6	....	...	+ Casts	120	60	88	—10	—15
5	5	72	13	11.9	25.7	2.16	72.7	1.5	..	1.25	.....	0.21	3.2	Albumin, trace	132	92	76	....	....
109	6	72	12	10.8	16.2	1.5	67	2	..	1.35	+55	0.47	...	..	100	60	88	+ 3	+16
2	7	69	9.8	12.9	26.1	2.02	74.2	...	..	3.5	—11	0.1	...	..	100	60	100	....	....
1	8	68	8.5	12.1	24.9	2	113	2	..	5	+ 7	1	...	..	132	74	80	+35	+52
90	9	60	7.6	11.4	14.5	1.34	68	2	..	1.75	— 8.3	0.44	4	..	122	54	67	+17	+40
86	15	58	3.8	12.6	15.9	1.26	94	1.5	..	1.75	+ 6.4	0.36	1.8	..	118	60	74	—12	—12
46	6	59	10	13.8	17.4	1.24	61	2.3	..	1.15	+13	1.7	2	..	140	82	76	+15	+37
149	10	54	5.4	10.1	17.4	1.72	82	?	..	1	+ 5	0.95	...	..	110	62	72	+10	+22
69	4	51	12.7	9.6	16	1.66	70	2.7	..	2	+ 4	1.9	2	..	140	48	84	0	+ 8
6	6.25	..	....	10.5	18.9	1.8	70.2	1.86	+	1.25	+29.5	0.3	4	Albumin, trace	120	60	72	....	....
Aver.	7.5	69	9.2	10.8	18.8	1.74	76	1.98	..	1.87	+ 8.5	0.79	3.5	..	120	64	80	+10.5	+22.5

the wide flare of the reaction to thyroxin was the only abnormality of the intracutaneous reactions, and the reaction to the Kromayer light was faint.

CASE 2.—A school boy, American, aged 12, had vasoneurosis and epilepsy. He showed active cardiac reflex, and marked mottling of the skin due to areas of vasoconstriction and vasodilatation. This patient is not to be considered as comparable with the others of the group, but has been, nevertheless, included because of the general interest of his case.

It is to be noted that: the calcium level was high and the K/Ca ratio normal; the Kromayer light erythema time was prolonged; the basal metabolic rate was low; the resistance of the skin to electric current was low, and the pulse rate was high. Microscopic examination of the capillaries of the skin showed marked dilatation.

CASE 1.—A medical student, Jewish, aged 23, was out of school because of a nervous breakdown. He had a tremor and felt weak.

It is to be noted that: the calcium level was high, but the K/Ca ratio was normal; the blood sugar level was high; the Kromayer light erythema time was delayed; the resistance of the skin to electric current was high; the reaction

to epinephrine was strongly positive, and the flare of the reaction to thyroxin was increased.

The remaining six patients had low capillary permeability.

Case 90.—A mail sorter, American, aged 30, was nervous (said that he got "rattled easily"). He was sensitive to venipuncture.

A low K/Ca ratio was the only outstanding abnormality.

Case 86.—A dentist, American, aged 50, had a "breakdown" four years prior to examination. He was suffering from alcoholism, was nervous, had lost his practice and was "down and out." Occasionally, he worked as a janitor. He had always been the most nervous one of his family. His mother had exophthalmic goiter. He had had angioneurotic edema when a student in 1900.

inations of a Group of Nervous Persons

CO_2 Combining Power	Endothelial Reaction	Heart	Tuberculosis	Influenza	Capillaries	Ice Reaction Time, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg.	Epinephrine Wheal (Diameter, Mm.)	Epinephrine, Flare (Radius, Mm.)	Morphine, Wheal (Diameter, Mm.)	Morphine, Flare (Radius, Mm.)	Thyroxin, Wheal (Diameter, Mm.)	Thyroxin, Flare (Radius, Mm.)	Caffein, Wheal (Diameter, Mm.)	Caffein, Flare (Radius, Mm.)
53.2	..	Sthenic	.....	+	Slight granulation	30	29	212	222	14.8	12.4	12.4	19.2	13.4	9	16.2	7
56.8	..	Sthenic	.....	+	Normal	20	22	210	158	20.4	10.2	11.8	17	15.2	7.6	10	10
....	..	Sthenic	Healed	+	+	18	26	183	145	12.4	3.2	8.2	1.6	20.2	0	25	0
63.9	..	Large	Healed	0	Normal	..	48	210									
51.4	..	Asthenic	.....	..	Normal	25	42	140	267	17.4	9	9	7.2	12	9.4	16.2	0
55.6	..	Asthenic	.....	..	Dilated												
62.1	..	.....	.....	..	Normal	25	23	202	158	20	8	12.4	16	13.2	9.6	12.2	0
57.9	..	Asthenic	0	..	Normal	10	30	192	222	18.4	11.6	10.4	20.2	12.2	0	27.4	0
55	..	Sthenic	.....	..	Normal	25	50	176	185	18.8	14	11.8	19.6	15.4	12.4	14.2	0
56.2	..	Asthenic	.....	+	Urinary disturbance	15	29	168	...	21.2	13.2	15	16.2	12.2	11.2	25.2	9.2
65.4	..	Sthenic	.....	+	Normal	15	35	209	215	20	9.6	15	7.4	19	0	26	10
54.8	..	Asthenic	Healed	+	Normal	20	22	160	...	21.2	10	12.2	22	14.4	10.2	30.4	2.6
61.1	..	Asthenic	.....	0	Normal	..	49	300									
57.8						20.4	33.6	198	196	18.3	10	11.6	14.6	14	6.8	18.6	3.8

It is to be noted that he had a prolonged blister time; a low K/Ca ratio; a high sugar level; a vagotonic reaction to epinephrine, and increased flares at the sites of injection of pharmacologic substances (except caffein).

Case 46.—A carpenter, American, aged 29, a poorly developed person (from insufficient nutrition), fainted on venipuncture. He was nervous and had headaches frequently. This person died a few months later at the Cook County Hospital from bronchopneumonia.

It is to be noted that he had a high calcium level with a low K/Ca ratio; a high resistance of the skin to electric current; relatively high blood pressure, with some evidence of abnormality of the capillaries of the skin, and an increase in the flares of the reactions to all the pharmacologic substances.

Case 149.—A plumber, American, aged 35, was nervous, had some night sweats and had lost some weight. Recently, he had been in financial difficulties. His mother had high blood pressure and was nervous.

It is to be noted that: The K/Ca ratio was low; the blood sugar was slightly increased; the resistance of the skin to electric current was high, and the blister time was prolonged.

Case 69.—A medical student, Jewish, aged 22, was nervous and had a tremor. He felt weak on venipuncture. He had had a duodenal ulcer since 1925. His father was nervous, with a blood pressure of 160 systolic and 170 diastolic. His mother also was nervous, and had a blood pressure of 210, with myocardial degeneration.

It is to be noted that he had a short blister time; a low K/Ca ratio; a high resistance of the skin to electric current; an increase in pulse pressure; marked flares in the reaction of the skin to the pharmacologic substances, and well marked clinical symptoms of the systemic reaction to epinephrine—pallor, headache, feeling of distress, etc.

Case 6.—A painter, Jewish, aged 49, was nervous, had vague pains and was occasionally dizzy, especially after eating. The blood pressure in November, 1926, was 160 systolic and 80 diastolic. There was a contraction in the visual fields indicating early optic atrophy (late neurosyphilis). The Wassermann reaction was positive. The roentgen examination of the chest indicated sclerosis of the aorta, and large heart. The patient died several months later from myocardial degeneration.

The low K/Ca ratio and an increase in the basal metabolic rate were the most prominent observations; there was a trace of albumin in the urine.

COMMENT

That the emotional states can alter the mineral metabolism was shown by Dresel.[16] Tómasson[17] also studied the correlation of mental excitation and the mineral balance. His studies, however, were made on psychopathic persons, as were the studies of Weston and Howard.[18]

When we review this small series of cases, the outstanding clinical complaint being nervousness (with the exception of case 2), the most striking observation in the blood seems to be an unusually low K/Ca ratio. Rather striking, too, is the relatively high resistance of the skin to electric current—in sharp contrast to the observations in the exophthalmic group.

On the other hand, these persons showed an increase in the red flare at the site of the injection of thyroxin, similar to that found in the patient with exophthalmos.

While the patient with exophthalmic goiter presented a fundamental autonomic disturbance, and seemingly a "thyroid factor" not necessarily associated with the same thyroid factor that increases the basal metabolic rate, the nervous patients presented mixed autonomic exaggerations, as well as varying reactions to epinephrine and an exaggeration of the flare due to thyroxin similar to that seen in the patients with exophthalmic goiter (and which is diminished after thyroidectomy). The differentiation of the so-called cases of "autonomic imbalance" from exophthalmic goiter has been discussed particularly by Kessel and

16. Dresel: Klin. Wchnschr. **33**:311, 1924.

17. Tómasson, Helgi: Blodets Elektrolyter, Copenhagen, Levín & Munksgaard, 1927.

18. Weston, P. G., and Howard, M. Q.: Determination of Sodium, Potassium, Calcium and Magnesium in Blood and Spinal Fluid in Manic-Depressive Insanity, Arch. Neurol. & Psychiat. **8**:179 (Aug.) 1922.

Hyman,[19] and Eason,[20] too, has covered the subject, so that we need not dwell on it here.

We can only suggest from these limited observations that the mineral balance of the "nervous" patient is apparently altered, so that the potassium values of the serum are sometimes low. With this there appears to be an increase in the capillary permeability. That the emotional state can apparently have some influence here is made probable from the following observations:

The person examined was one of the hospital technicians, a man, aged 40, highly intelligent and normal on physical examination. He was first examined in December, 1926. At this period, his blister time was found to be six hours, and his capillary permeability 80. The pulse rate was between 68 and 72; the blood pressure was 120 systolic and 70 diastolic with a negligible effect following the injection of epinephrine hydrochloride. The basal metabolic rate was —12.

He was reexamined in June, 1927. At this time the blister time was five hours and the capillary permeability had diminished to 64; the blood pressure had diminished to 112 systolic and 70 diastolic.

We were at a complete loss to account for the high permeability of the capillaries first noted, until a subsequent history was given us by this person to the effect that during the time of the first examination he was in the process of losing his entire savings in a stock venture and was naturally under great mental strain.

CONCLUSIONS

Observations made on a small series of patients with exophthalmos reveal the following changes: shortened blister time, increased capillary permeability, lower resistance of the skin to electric current, increased serum globulins, increased serum calcium with a normal K/Ca ratio and a lower carbon dioxide combining power.

After operation, a reversal of these reactions usually occurs.

The reactivity of the skin to injections of the pharmacologic substances reveals definite changes before and after operation, involving particularly the reactions to epinephrine, morphine and thyroxin.

From an analysis of the postoperative reactions in individual cases, we believe that factors other than those responsible for the increase in the basal metabolic rate must be considered in the exophthalmic complex.

The so-called "nervous" patients of our series appear to have an associated or underlying change in the K/Ca ratio and the group has a low potassium level. In general, the capillaries of the group are more permeable, but there are individual exceptions. They resemble the patients with exophthalmos, too, in the degree of their reactivity to thyroxin. They differ markedly in having a higher resistance of the skin to electric current.

19. Kessel, L., and Hyman, H. T.: Am. J. M. Sc. **165**:513, 1923; Studies of Exophthalmic Goiter and Involuntary Nervous System; Diagnosis of Exophthalmic Goiter, J. A. M. A. **88**:1478 (May 7) 1927.

20. Eason, John: Exophthalmic Goiter, New York, The Macmillan Company, 1927.

VI. PATIENTS WITH GLAUCOMA AND THEIR VASCULAR REACTIONS *

During the course of work which Goldenburg [1] carried out in connection with glaucoma, the conclusion was reached that the inherent cause lies in alterations of the capillaries of the ciliary body, these alterations consisting of an increase in permeability (probably associated with an increased metabolic activity of the cells of the ciliary body) with a resulting swelling of the body, a coincident shutting of the canal of Schlemm and an increase in the pressure of the aqueous as a result of the continued production of the fluid with diminished possibilities of its proper removal. It is our opinion that these alterations may take place rapidly and particularly in persons who are constitutionally so oriented, the capillaries of the body are more labile. That the vessels of the eye may show such sudden swelling of the endothelium has been observed by Lenaz [2] in a case in which the endothelial occlusion in an arterial branch was so great that an embolus was suspected.

Endothelial instability is found associated with certain endocrine or autonomic disturbances, which only in recent years have been studied more intensively. In the group showing this association are included persons with urticaria, angioneurotic edema, hay-fever, asthma, migraine and mucous colitis, conditions in all of which distinct alterations may occur in the ionic equilibrium (particularly the K/Ca ratio, CO_2 combining power, cholesterol content, etc.), alterations not yet fully explainable. To this group must be added the persons with hyperpiesis, as well as the ones with hypotension—which, according to Kylin,[3] are merely different clinical responses to the same basic alteration.

During the course of the study we felt it might be of some interest to examine patients with glaucoma with particular reference to the blood chemistry, the general reactions of the skin and the vascular condition (microscopic examination of the capillaries of the skin, roentgen examination of thoracic vessels, examination of the urine, etc.).

We have examined in detail fourteen patients of the Illinois Charitable Eye and Ear Infirmary. The histories of these patients are briefly

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* In collaboration with Dr. Michael Goldenburg, Illinois Charitable Eye and Ear Infirmary, and Dr. Louis Parmacek.

1. Goldenburg, Michael: Illinois M. J. **52**:474, 1927.
2. Lenaz, L.: Wien. klin. Wchnschr. **39**:1015, 1926.
3. Kylin, E.: Acta med. Scandinav., 1927, supp. 19, p. 1.

set forth in table 1. In making the examinations, we have carried out the routine described in part 1.[4]

When we so analyzed our small series we found that every one presented definite evidence of alteration referable to the vascular system.

Of the two patients who had syphilis, no. 145 had distinct granulations in the capillaries of the skin, albumin in the urine and, as revealed by an x-ray picture of the chest, syphilitic aortitis; no. 164 had granular casts in the urine, and the x-ray picture revealed syphilitic aortitis.

Of the three patients who had high blood pressure, no. 154 (whose blood pressure was 190 systolic and 118 diastolic) revealed an arteriosclerosis of the aorta on roentgen examination, and granulations of the capillaries of the skin. No. 170 (whose blood pressure was 188 systolic and 96 diastolic) with a blood sugar content of 320 Mg. and a basal metabolic rate of + 33, had a pulse rate of 104, and the roentgen examination showed a definite sclerosis of the aorta. No. 165 (whose blood pressure was 170 systolic and 100 diastolic) had hyaline casts in the urine and a pulse rate of 110; roentgen examination showed an enlarged heart and a dilated aorta. The rest of the patients had blood pressure within the normal range. Of these, no. 150 had hyaline casts in the urine and gave roentgenologic evidence of pulmonary fibrosis; no. 153 had granular casts in the urine and gave roentgenologic evidence of arteriosclerosis, as well as of fluid in the chest. No. 137 had albumin in the urine, and the capillaries of the skin showed distinct dilatations. No. 140 had albumin in the urine and suffered from hay-fever; the roentgenogram of the chest indicated some activity at the right upper apex. No. 141 had albumin in the urine, and the capillaries of the skin showed marked granulations. No. 161 had albumin in the urine, and the capillaries of the skin showed marked dilatations. No. 148 gave a history of cerebral hemorrhage; the roentgenogram indicated a marked sclerosis of the larger thoracic vessels, and the capillaries of the skin showed marked granulation. No. 160 had asthma; in addition, the roentgenogram indicated a dilatation of the aorta, with arteriosclerosis, and with fibrosis and atelectasis of the lungs. No. 167 had low CO_2 combining power, in addition to the highest sensitivity to epinephrine observed in the group. The capillaries of the skin revealed no marked changes The roentgen examination indicated an old pulmonary fibrosis and bronchiectasis.

4. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, Arch. Int. Med. **38**:663 (Nov.) 1926.

TABLE 1.—*The Clinical Histories of Patients with Glaucoma*

Case	Sex	Occupation	History of Clinical Picture	Vision	Tension Schirtz	Type	Date of Operation	Tension After Operation	Later Tension	Last Vision	Complications
137	F	Housewife	2/3/27; pain in right eye for week; headache above orbit; lacrimation and photophobia; lids normal; conjunctiva injected; iris normal; pupil contracted; cornea cloudy and stippled; anterior chamber shallow	R. Had more at 18″ L. 20/30	R. 65 L. 15	Acute congestive (or inflammatory)	2/8/27 iridotasis	R. 25 L. 15	R. 30 L. 17¼	..... As before	Reoperation necessary
140	M	Laborer	One year ago left eye was painful, but recovered without treatment; 9 months ago foreign body in left eye—although eye was not very sore, vision was bad; 3 weeks ago eye so painful patient had to stop work; eye injected, pupil dilated, cornea steamy and insensitive; hay-fever	R. 20/25 L. No light perception or projection	R. 12½ L. 45½	Acute attack superimposed on chronic congestive glaucoma	8/16/27 iridotasis	.....	.....	.....	
141	F	Housewife	Trouble in left eye 3 or 4 years ago; vision gradually failed; not always painful; pain severe now and located in top of head; right anterior chamber shallow; pupil dilated and not reactive to light; marked cup; left scleral staphyloma at 12 o'clock; iris drawn into staphyloma; pupil oval and not reactive to light; anterior chamber shallow; iris cloudy; fundus invisible	R. 20/100 L. Had more	R. 36¼ L. 50¾	Chronic congestive	Trephine	24	.....	.....	
145	M	None	Gradually failing vision for about 4 or 5 months; cataract	R. 20/100 L. Fingers at 3 feet	R. 16 L. 40	L. Noncongestive (simplex)	8/2/27 iridotasis	Down to markedly improved	.....	.....	R. Incipient cataract, central choroiditis L. Cupping of disk
148	F	None	Chronic glaucoma in both eyes for several years; right operated on 3 years ago, became worse and later enucleated; left pupil dilated; cornea steamy; vitiligo; old cerebrohemorrhage	R. Enucleated, had more	L. 32	Chronic congestive	9/6/27 iridotasis	.....	.... ..	.....	
150	M	Teamster	Right enucleated; left hurt 3 weeks ago with iron object; became fluid in 3 days; later cleared up; later vision became foggy; some pain; slight injection of left conjunctiva; cornea and iris normal; pupil regular; anterior chamber shallow; deep cupping of disk	R. Enucleated, 20/50	L. 54	Noncongestive	3/1/27 iridotasis; could not reduce iris with exercise	.....	.....	With glasses, 20/30	
153	M	Farmer	Vision slowly failing for past 4 or 5 years; no pain; right pupil dilated, cornea steamy; anterior chamber shallow; left pupil dilated; anterior chamber shallow; cataract	R. Perception and projection poor with bright light L. Very poor with bright light	R. 52 L. 48	Noncongestive Noncongestive	R. 4/13 L. 9/20 iridotasis, both eyes	11/2/27 R. 43 ? L. 52 ?	.. ....	.....	R. Central opacity of lens L. Larger central opacity of lens; transillumination negative

154	M	Laborer	Severe pain over right eye 2 weeks ago; similar attack 2 years ago; vision good until 2 weeks ago; then it began to fail with pain in head; conjunctiva congested; some ciliary injection; cornea hazy; pupil does not react to light; anterior chamber fairly normal	R. 20/200	R. 61	Acute congestive	10/28/27 trephine	.....	.....	.....	Tension went up to 83 under physostigmin and $MgSO_4$; by proctocylosis; 11/17/27, enucleation
160	M	Laborer	"Terrible" pain over right eye; patient unable to see; asthma	R. Fingers at 4 feet L. 20/40	.....	Acute congestive	9/12/27 deep iridectomy 10/18/27 iridectomy enlarged	9/26/27, 36	.....	.....	
161	F	Housewife	Vision failing for past 3 or 4 years; occasional pain on right side of head; pupil widely dilated; anterior chamber shallow and lenz hazy; fundus indistinct; vessels of sclera dark, tortuous; marked cup; optic atrophy; left normal; scleral vessels dilated	.....	R. 50 L. 20	Chronic congestive	10/18/27 iridotasis 12/6/27 iridotasis	R. 25½ L. 16 12/6/27, 7¼	12/5/27 30 1/16/27 R. 12¼ L. 18½	.....	
164	M	Insurance agent	Pain in last 4 months in right eye and side of head; pupil dilated; cornea hazy; anterior chamber deep	.....	R. 42¾ L. Normal	Acute congestive probably secondary	9/29/27 anterior sclerotomy 11/1/27 iridotasis	11/12/27 16	.....	.....	Wassermann reaction of blood ++++
167	F	Housewife	Vision failing for years; under care of Christian science practitioner; right cornea abraded; insensitive opacity of iris; left the same	R. Light perception L. Same	R. 16 L. 42¾	R. Cataract L. Cataract with tension congestive glaucoma	11/15/27 iridotasis	.....	.....	.....	11/22/27. Extraction of cataract; lens adherent to lens fossa, but got it anteriorly with iris forceps 11/23/27, 8:30 p. m., choroidal hemorrhage 11/20/27. Enucleation
165	M	Laborer	Vision failing for year; occasional pain along side of head; both pupils dilated; anterior chambers shallow; corneas stippled	R. 2/200 L. 1/200	R. 70 L. 70	Noncongestive	10/18/27 iridotasis, both eyes	12/16/27 R. 20 L. 26	2/21/28 R. 18¾ L. 18½	2/28/27 R. 4/200 L. Perception of light	
170	F	None	Vision in left eye began failing in June, 1923; in September vision in left eye completely lost; vision in right eye began failing about the same time and was lost in April, 1927; anterior chamber fairly good; pupils dilated eccentrically; new vessels formed on iris; some postsynechia; cornea hazy; arcus similarly marked; opacity of both lenses	No light perception in either eye	R. 80¼ L. 85⅛	Noncongestive	12/13/27 iridotasis, right eye 1/17/28 iridotasis, left eye	2/15/28 R. 40½ L. 13½	3/15/28 R. 42 L. 26	Results not good	Could not incarcerate iris well owing to synechia; profuse hemorrhage; blood sugar from 300 to 350 mg.; after anterior chamber was emptied, tension did not go down

The details of the study are collected in table 2. Immediately below the averages of these details, we have tabulated the averages obtained in examinations of thirty-seven normal persons, for comparison. These thirty-seven were normal persons and persons with roentgenologic evidence of healed parenchymal tuberculosis (part 2).

In all the cases of this small series, we have established that there are definite vascular alterations, in the form of urinary changes, changes

TABLE 2.—*The Results of Correlative Examinations of Fourteen Patients with Glaucoma;*

Individual Number	Blister Time, Hours	Permeability of Capillaries, %	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / C Ratio	Sugar, Mg.	Globulin, per Cent	Wassermann Reaction	Kromayer Light Erythema Time, Hours	Basal Metabolic Rate	Skin Resistance (Electric)	Changes in Urine	Blood Pressure, Systolic	Blood Pressure, Diastolic	Pulse Rate	Epinephrine Reaction, Pulse Pressure, %	Epinephrine Reaction, Pulse Pressure × Pulse Rate, %	CO_2 Combining Power
137	15	61	4	8.1	18.2	2.24	73	37	..	2	3.6	1.9	Trace of albumin	119	67	78	+ 7	+ 9	51.9
140	0	68	0	11.4	29.7	2.61	82	37	..	2½	....	0.45	Trace of albumin	100	70	68	+10	+10	55.6
141	..	..	..	9	28.2	3.13	86	..	..	2	....	0.2	+	118	78	84	+ 9	0	64.6
145	15	66	4.4	10.1	15.7	1.55	70	55	+++	2¾	+19	0.35	Trace of albumin	136	80	84	+43	+43	55.4
148	15	56	3.7	9.7	24.3	2.50	79	24	..	1½	+17	0.26	.....	116	74	90	+ 8	+18	69.5
150	15	57	3.7	12	21.3	1.78	82	15	..	1½	+39	0.22	Hyaline casts	140	86	84	+ 6	+ 6	62.7
153	15	78	5	9	18.7	2.08	83	0	..	1½	+ 2	0.15	Granular casts	124	58	64	+10	+10	62.2
154	15	60	4	....	23.08	....	71	3	..	1½	+18	0.09	?	194	118	68	....	....	56.6
160	15	66	4.4	10.86	21.58	1.98	65	44	..	1⅛	+16	0.4	?	128	64	68	+ 8	+28	62.7
161	5	72	14	9.17	18.03	1.96	86	20	..	1¼	16	1.4	Trace of albumin	107	64	88	+25	+51	49.4
164	9	71	8	8.7	16.54	1.89	65	20	+++	2¾	— 4.7	0.23	Granular casts	110	76	80	+14	+35	55.9
165	11	60	5.5	10	17.94	1.79	80	16	..	1⅓	+ 0.5	0.18	Hyaline casts	170	100	110	....	....	53.9
167	15	56	3.7	12	22.72	1.9	81	27	..	2	0.7	0.85	.....	137	92	84	62	80	47.9
170	15	72	5	10.58	23.71	2.2	320	36	..	...	+33	0.07	.....	188	96	104	....	....	52.5
Averages*	13.3	64	4.8	10	21.4	2.14	77	25	2+	1⅘	+12.4	0.48	.....	134	80	82	+18	+29	57.2
Averages†	7	63.3	9.4	10.1	20.6	2.04	71.3	30		2	+ 6.3	0.35	.....	116	69	71	+16.5	+24	58

* For 14 patients with glaucoma.
† For 37 normal persons.

in the capillaries of the skin, increased blood pressure, sclerosis of the larger thoracic vessels, or a history of disease known to be associated with autonomic vascular disturbances (asthma, hay-fever).

The intracutaneous reactions may also be interpreted in this direction. Thus, the flare of the reaction to morphine is diminished, and the flare of the reaction to caffeine and that of the reaction to thyroxin are absent. The wheal in the reaction to epinephrine, on the other hand, is diminished. The wheal in the reaction to thyroxin is increased.

Comparison of the Averages of These Results with the Averages for Thirty-Seven Normal Persons

Endothelial Reaction (Rumpel-Leede)	Roentgen Examination of Chest: Heart	Roentgen Examination of Chest: Tuberculosis	Capillaries of the Skin (Microscopic Examination)	Reaction to Ice, Seconds	Age	Weight / Length	Cholesterol, Mg.	Intracutaneous Reactions: Epinephrine, Wheal, Mm.	Epinephrine, Flare, Mm.	Morphine, Wheal, Mm.	Morphine, Flare, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Caffein, Wheal, Mm.	Caffein, Flare, Mm.	X-Ray Diagnosis
..	Asthenic	.....	Dilatation	30	61	166	222	15.4	11	13.5	10	13	0	18	0	
..	Asthenic	+	.....	40	45	...	158	18	8	11	10.7	27	0	30	0	Active tuberculosis of right upper lobe
+	Sthenic	.....	Granulation	15	48	...	267	17.4	7.7	9	7	10	13	22	0	
..	Sthenic	.....	Granulation	20	71	166	208	18	13.6	16	0	16	0	23	0	Syphilitic aortitis
..	Asthenic	Fibrosis	Granulation	10	67	182	317	18	12	9.7	0	17	0	18	0	Arteriosclerosis (aorta)
..	Sthenic	Fibrosis	.....	7	67	238	247	17	14	18.5	9.5	16	0	22	0	Pulmonary fibrosis
..	Sthenic	Healed parenchymal	Diminished dilatation	30	75	223	175	22	6.5	9.5	0	18	0	22	0	Slight arteriosclerosis; fluid in chest
..	Asthenic	.....	Granulation	20	55	181	180	23	10	13.5	0	26	0	28	0	Arteriosclerosis (aorta)
..	Sthenic	Healed parenchymal; fibrosis	Normal	10	58	181	190	16	8	12	0	20	0	24	0	Arteriosclerosis (aorta); bronchiectasis; emphysema
..	Sthenic	.....	Dilatation	12	43	171	208	14	13	5.5	10.7	13	0	20	0	
..	Sthenic	Healed parenchymal	.....	15	48	223	185	18	14.7	17	12.5	(Not done)				Syphilitic aortitis
..	Sthenic	.....	.....	5	52	250	185	17	13	10	13.7	25	0	31	0	Hypertrophy of heart; dilatation of aorta
..	Asthenic	.....	Dilatation	5	77	158	256	17	14.25	12	9	15	0	18	0	Scoliosis; bronchiectasis
..	Sthenic	.....	.....	..	56	247	170				(Not done)					Arteriosclerosis (aorta); bronchiectasis
..	.....	.....	.....	15.6	58.7	199	212	17.7	11.2	12.1	6.4	18	1	23	0	
..	.....	.....	.....	15.5	41.8	221	228	20	9	11.3	16.2	11.4	5.8	17.4	2.38	

VII. SENSITIZED PERSONS AND PERSONS WITH DISEASES OF THE SKIN

ANGIONEUROTIC EDEMA

CASE 152.—A white man, American, aged 27, had a swelling of the scrotum two years prior to the examination. The swelling lasted one day and returned at intervals of from three to four months for one year. During a remission, the patient received tetanus antitoxin. Four days later, his throat and tongue were involved. Two months later, the same kind of attack occurred. The last attack had lasted six days and was disappearing at the time of the examination.

The father had had angioneurotic edema for ten years. The mother once had urticaria. Two aunts had epilepsy. The patient had suffered at various times from attacks of migraine and was sensitive to strawberries.

This patient, it is to be noted, had a short blister time, with increased capillary permeability, a distinctly vagotonic reaction to epinephrine and diminished flares of the reactions to epinephrine and morphine with increased flares of the reactions to thyroxin and caffein.

CASE 38.—A young Jewish druggist, aged 35, with a history of angioneurotic edema, had three sisters, one of whom had epilepsy, one of whom was nervous and one of whom was seemingly well. The father was 70 years of age and well. The mother was 65 years of age and suffered from neurasthenia. This patient formerly had a typical Sunday migraine. At the time of examination, he had pruritis, and was sensitive to raspberries. Formerly, ingestion of milk caused cramps and diarrhea. Watermelon still had this effect. At the time of examination, he was without angioneurotic manifestation.

As in the previous case, we find the patient in this case showing a short blister time with somewhat increased capillary permeability, but no chemical changes. The systolic reaction to epinephrine was vagotonic, but the pulse pressure showed an increase immediately after the injection. The capillaries of the skin appeared swollen and were markedly red, and in some a distinct granulation became apparent. The flares of the intracutaneous reactions (except of that to epinephrine) were all increased.

URTICARIA

CASE 171.—Menstrual Urticaria: A young woman, Jewish, aged 23, a laboratory worker, was alert, nervous and rather irritable. Her family history was negative except in relation to tuberculosis. The grandfather had had tuberculosis, and the mother died of tuberculosis. The patient had malaria in 1921. At the time of the examination, she had slight mitral insufficiency. She had had a rather irregular menstrual course. The urticaria, which was generalized, began one or two days before the menstrual period, and lasted approximately a week. The patient was then free from urticaria during the intermenstrual period. The patient recently had had a curettage and since then had been free from disturbance.

The comparison of the observations during the menstrual period with the intermenstrual observations is of interest. During the menstrual period, the permeability of the capillaries was increased, the potassium level, as well as the

K/Ca ratio, was lowered, there was less cholesterol and the systolic blood pressure and the pulse rate were higher. The reaction to epinephrine was sympatheticotonic during both periods, more so during the intermenstrual time, when, too, the intracutaneous reaction to epinephrine was more marked. The wheals of the reactions to thyroxin and caffein were larger than normal at both times.

Case 116.—A young Irish woman, aged 30, came to America four years prior to the examination. The first attack of urticaria appeared two years before the examination, when she had angioneurotic edema. Two months before, her father died of pernicious anemia and the attack in question dated from this time. The urticaria was worse at night and because of the interference with sleep the patient was rather nervous. The family history was negative. On general physical examination, the spleen was found enlarged, the icteric index was increased and bile was also present in the urine. With minor exceptions, the urticaria had persisted to the time of examination. No definite sensitization could be determined, but the skin was particularly sensitive to staphylococci The function of the reticulo-endothelial system, as determined by administration of a vegetable oil (oleokinol), seemed practically normal.

The results of the examination were as follows: A strikingly short blister time, low permeability of the capillaries and a distinctly vagotonic reaction to epinephrine with the pulse pressure much increased. The results of all the chemical examinations were within the normal limits.

Case 139.—A stenographer, American, aged 29, had vitiligo for ten years and urticaria for some eight weeks. She had jaundice at the age of 11, for two weeks. Of late, she had been nervous, with occasional palpitation. She had a nervous breakdown at the age of 19. She felt "shaky" when she worked hard, but had suffered no loss of weight. One other sister had vitiligo and one had diabetes. The urticaria was made worse by pineapple, popcorn and watermelon.

Practically the only abnormalities were that found in the pulse rate and the vagotonic reaction to epinephrine. There was a trace of albumin in the urine. The intracutaneous reactions to epinephrine and morphine showed lessened wheals and those to thyroxin and caffein increased wheals and flares. The patient was treated with calcium for two months. On reexamination, the blister time was somewhat shortened, the permeability of the capillaries was increased and the calcium was lower. During this time, however, the patient was somewhat improved.

ECZEMA

Case 101.—A laborer, aged 55, born in Scotland, one of our group of 100 normal men, had chronic eczema of the legs. He had a history of moderate alcoholism. The family history was negative, except that one uncle had epilepsy. The patient was rather stolid and seemingly unemotional. Fifteen years prior to the examination, he had had rather severe diarrhea and with it urticaria.

The examination of this patient revealed merely a low capillary permeability together with a diminished intracutaneous reactivity to morphine. The reaction to epinephrine was sympatheticotonic.

Case 132.—The clinical history of the patient, the most interesting of the entire group of patients, has been described. It is to be recalled that he had the lowest K/Ca ratio of all the patients, the lowest CO_2 combining power and

increased muscle reactivity. The cholesterol level was high, the Kromayer light erythema faint, the pulse rate slow and the reaction to epinephrine vagotonic. The wheals of the reactions to thyroxin and caffein were somewhat increased.

The results of the examination of this patient emphasize the impossibility of schematizing the results and the futility of endeavoring to place these persons in hard and fast groups. The patient was typically vagotonic, but, in addition, he was suffering from a relative acidosis. Despite this acidosis, the muscular irritability was high.

GASTRO-INTESTINAL SENSITIZATION

CASE 54.—A man, American, aged 49, showed a trace of albumin in the urine and x-ray evidence of myocarditis and sclerosis. He was sensitive to peaches and strawberries (urticaria). The reaction to epinephrine (systolic) was distinctly vagotonic, but the pulse rate was sympatheticotonic.

CASE 172.—A Greek, aged 30, who had had a positive Wassermann reaction in 1921, had Raynaud's disease. The family history was negative. The calcium level was high (low K/Ca ratio), the reactions to the Kromayer light and ice were faint, the blood pressure was low and the reaction to epinephrine was markedly sympatheticotonic. All intracutaneous reactions to the pharmacologic substances injected were marked. The patient was sensitive to peaches and cherries.

CASE 169.—The patient had Buerger's disease (Wassermann reaction ++++). He showed a high calcium level with a low K/Ca ratio. The serum proteins were concentrated, the reaction to Kromayer light was faint and the reaction to epinephrine (systolic) was vagotonic. The flares of all the intracutaneous reactions (except that to epinephrine) were absent. The patient was sensitive to strawberries.

CASE 14.—A German, aged 36, an artisan, had albumin and casts in the urine, together with an undetermined reducing substance (not dextrose). He probably had gallbladder disease. He was sensitive to honey and pineapple; these caused intense pain. The capillaries of the skin were increased in number, and their permeability was high. The calcium level was high and the K/Ca ratio was low. The cholesterol level was also high and the reactions to the Kromayer light and ice were faint. The reaction to epinephrine was vagotonic. The wheal of the reaction to epinephrine was increased and the flare diminished.

PURPURA

CASE 120.—A Hungarian woman, who gave a history of sensitiveness to tomatoes, on admission had petechial hemorrhages over the body and the extremities, showers appearing at intervals of from twenty-four to forty-eight hours. There was considerable blood in the urine. It may be noticed that the permeability of the capillaries was high and the endothelial reaction (Rumpel-Leede) was positive. The blood chemistry was normal, except for an increase in the globulins. Microscopic examination revealed distinct granulations of the skin capillaries.

PREVIOUS SENSITIZATION—HAY-FEVER

CASE 128.—An American workman, of Irish parentage, aged 66, stated that he had had hay-fever for years. In addition, he had an enlarged prostate and

x-ray evidence of arteriosclerosis of the larger vessels. The capillaries of the skin showed distinct granulations and the urine contained albumin. The blood chemistry was practically normal.

CASE 148.—A white woman, aged 67, had glaucoma and vitiligo. She had had hay-fever twenty-five years prior to the examination and had had urticaria. X-ray examination of the chest showed considerable healed pulmonary tuberculosis and arteriosclerosis, and she gave a history of having had cerebral hemorrhages. The capillaries of the skin showed granulations; the reaction to epinephrine was vagotonic.

CASE 140.—A white man, aged 45, suffering from alcoholism and glaucoma, had a history of hay-fever every spring. There was roentgenologic evidence of active tuberculosis. Examination of the capillaries of the skin showed dilatations, but the total number was diminished. There was a trace of albumin in the urine and the reaction to epinephrine was vagotonic.

CASE 93.—An American workman, aged 53, a periodic drinker, had a history of hay-fever every fall (ragweed). In addition, he was sensitive to halibut. He was short of breath and the x-ray picture indicated a myocarditis. The reaction to epinephrine was vagotonic; the capillaries appeared to be normal.

CASE 160.—A white man, American, aged 58, was suffering from glaucoma. He gave a history of asthma extending over many years. An x-ray picture of the chest indicated emphysema and bronchiectasis, together with arteriosclerosis of the larger vessels. The reaction to epinephrine was vagotonic. The capillaries appeared to be unchanged.

CASE 36.—A white man, American, aged 43, had an attack of hay-fever four or five years prior to the examination. The reaction to epinephrine was vagotonic, and there was a trace of albumin in the urine.

All the members of this group showed relatively high K/Ca ratios, CO_2 combining power within normal limits and faint reactions to the Kromayer light. Their blood pressures were relatively low and their pulse rates were somewhat increased.

PREVIOUS SENSITIZATION—URTICARIA AND ANGIONEUROTIC EDEMA

CASE 45.—An American workman, aged 39, had a history of scarlet fever with involvement of the kidneys at the age of 4. The blood pressure was 162 systolic and 114 diastolic. The reaction to epinephrine was vagotonic. The patient had had urticaria twenty years before.

CASE 86.—A former dentist, aged 50, was extremely nervous, with a history of alcoholism. He had had angioneurotic edema twenty-five years before. The reaction to epinephrine was vagotonic.

CASE 56.—An American workman, aged 44, had x-ray evidence of active pulmonary tuberculosis. He had had angioneurotic edema and dermographia three years before. The reaction to epinephrine was vagotonic.

CASE 77.—An American workman, aged 39, formerly suffered from alcoholism. His grandfather had asthma. He stated that he had sugar in the urine and that ten years ago he had urticaria from eating sweet potatoes. The patient was

nervous. He gave a vagotonic reaction to epinephrine and a positive endothelial reaction (Rumpel-Leede).

CASE 80.—An American workman, aged 29, was nervous and had a distinct tremor. He had had urticaria three years before. He gave a distinct vagotonic reaction to epinephrine.

The Results of Correlative

Patient	Diagnosis	Blister Time, Hours	Capillary Permeability, %	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K / Ca Ratio	Sugar, Mg.	Protein, Mg.	Globulin, Mg.	CO_2 Combining Power	Cholesterol, Mg.	Kromayer Light Erythema Time, Min.	Skin Resistance	Ice Reaction	Basal Metabolic Rate	Blood Pressure: Systolic	Blood Pressure: Diastolic	Pulse Rate	Reaction to Epinephrine: Pulse Pressure, %	Reaction to Epinephrine: Systolic	Weight/Length Ratio
152	Angioneurotic edema	4	73	18	9.8	20.1	2.05	63	7.47	20	63.4	175	60	0.18	15	4.8	120	74	80	—5	Vagotonic	243
38	Angioneurotic edema	5	69	14	9.8	21	2.14	86	8.28	40	58.5	...	90	0.29	10	11.5	124	65	84	+31	Vagotonic	194
171	Menstrual urticaria	5	73	14	12.6	17.9	1.42	72	....	....	48.7	202	75 (faint)	0.08	20	8	114	66	96	+18	Sympathetic-cotonic	160
	(Intermenstrual observations)	6	64	10	12.6	21.3	1.68	64	7.41	....	46	230	...	0.08	..	12	102	68	68	+100	Sympathetic-cotonic	160
116	Urticaria	3½	60	17	10	19.4	1.94	78	6.98	40	55.1	175	30	0.60	20	9	128	50	80	—17	Vagotonic	195
139	Urticaria and vitiligo	6	65	11	9.7	18.4	1.9	81	7.10	18	50	175	120	0.20	8	5	113	71	104	+12	Vagotonic	176
		4½	68.5	15	8.6	18.7	2.1	78	7.95	....	50	190										
101*	Eczema	8¾	47	5.4	9.4	19.4	2.06	65	7.20	45	57.4	158	90	0.13	15	31	132	76	67	+13	Sympathetic-cotonic	191
132	Eczema	6	68	11.3	13.4	15	1.12	67	7.30	23	40.3	256	120 (faint)	0.31	10	—1.2	132	78	56	0	Vagotonic	234
54*	Sensitized	6	60	10	....	22	....	80	8.28	33	56.6	...	75	0.26	25	—3.4	108	68	72	+90	Vagotonic	256
172	Sensitized	12	72	6	13	21.3	1.64	76	8.16	....	....	...	105 (faint)	0.08	45 (faint)	—18	108	78	94	+90	Sympathetic-cotonic	166
169	Sensitized	15	62	4.1	12.3	19.24	1.56	67	9.87	20	55.1	158	120 (faint)	0.23	25	—7	118	78	82	+40	Vagotonic	...
14*	Sensitized	7	74	10.5	11.2	19.6	1.75	67	8.06	37	65	278	95 (faint)	0.20	40	2.7	128	80	76	0	Vagotonic	198
120	Purpura	6	82	13	10	19.9	1.99	71	7.95	50	52.2	185	70	....	14	—5	...	..	...	....	.....	172
128*	Hay-fever for years	15	68	3.8	10.2	19.7	1.93	79	8.06	55	58.1	230	240	1	24	—18	122	70	84	+24	Vagotonic	186
148	Glaucoma	15	56	3.7	9.7	24.3	2.5	79	7.97	24	69.5	317	85 (faint)	0.26	10	+17	114	72	94	+18	Vagotonic	182
140	Glaucoma	15	68	4.05	11.4	29.7	2.61	82	6.25	37.5	55.6	158	150 (faint)	0.45	40 (faint)	.....	100	70	70	+10	Vagotonic	...
93*	.....	6	50	8.3	7.6	24.5	3.22	70	8.59	42	57	230	90	0.25	12	0	113	71	86	+19	Vagotonic	267
160	Glaucoma	15	66	4.4	10.86	21.58	1.98	65	8.16	44	62.7	190	70	0.4	10	+16	128	64	68	—28	Vagotonic	190
36*	Cardiovascular renal disease	8	58	7.2	12.1	26.3	2.17	90	8.28	33	57.6	...	120	0.11	20	+1.3	104	50	84	+28	Vagotonic	227
45*	Cardiovascular renal disease	6	54	9	11.2	16.6	1.48	77	7.73	40	54.3	...	45	0.28	20	+20	162	114	84	+8	Vagotonic	317
86*	Nervous	15	58	3.8	12.6	15.9	1.26	94	6.33	40	55	185	105	0.36	25	+6.4	118	60	74	—14	Vagotonic	176
56*	(Roentgen evidence) tuberculosis	6	61	10	9.8	28.6	2.52	65	9.36	35	56.6	...	135	0.32	15	—17.9	124	88	80	+22	Vagotonic	247
77*	Nervous	9	87	10	10.8	15.6	1.44	71	6.98	36	60.6	196	240	1	35	+7.9	126	78	82	+7	Vagotonic	187
80*	Nervous	6	91	15.1	8	13.7	1.7	69	8.28	33	53.2	222	100	1.6	30	+13	116	68	64	+12	Vagotonic	212

* The patient belonged to the group of 100 so-called "normal" men.

COMMENT

When considering the results of the examination of the group of persons who were presumably sensitized, it must be kept in mind that one can hardly expect distinct chemical alterations in conditions in which the clinical manifestations were so frequently evanescent and transitory,

Nathan and Stern[1] rightly emphasized that a single determination of the K/Ca ratio—for instance, during the course of a dermatosis—hardly gives a true picture, typical for the disease. One must make repeated determinations in order to obtain a true insight into the fluctua-

Examinations of Sensitized Persons

Changes in Capillaries	Arteriosclerosis, X-Ray	Healed Tuberculosis	Active Tuberculosis	Changes in Urine	Intracutaneous Reactions: Epinephrine Wheal, Mm.	Epinephrine Flare, Mm.	Morphine Wheal, Mm.	Morphine Flare, Mm.	Thyroxin Wheal, Mm.	Thyroxin Flare, Mm.	Caffein Wheal, Mm.	Caffein Flare, Mm.	Endothelial Reaction	Age	Sex	Associated Conditions and History
.....	..	..	..	Hyaline casts	26	7.5	9.5	10	9	8	9	10	..	27	M	
Dilatations, granulations	..	..	..	.....	18	8.6	8.8	25.4	10.2	10.4	4.8	11.6	..	39	M	
Dilatations	..	+	..	Albumin, faint trace	17.5	10.5	12.5	0	18	0	20	0	..	23	F	
Dilatations	..	+	..	.....	26	6.5	10	12.2	20	0	17	8	..	23	F	
.....	..	..	..	Bile	20.4	7.4	9.2	·8	5	0	18.2	0	..	30	F	
Dilatations	..	..	..	Albumin, faint trace	16	11	9.5	7.5	14	12.5	14	12	..	29	F	
Dilatations	..	+	..	.....	19.6	7	10.2	6	10	0	18.4	0	+	55	M	
Dilatations	..	+	..	.....	18.4	9.4	14.6	17.6	13.4	5	22,6	6	..	26	M	
.....	..	..	..	Albumin, trace	21.2	10.4	11	18	12	0	11	0	..	49	M	Sensitization to peaches and strawberries; cirrhosis probable
Dilatations	..	+	..	.....	22.4	16	15.5	8.5	18	16	20	7.5	..	30	M	Raynaud's disease; syphilis, 1921; sensitization to peaches and cherries
Retina pale	..	+	..	.....	20.8	11	13	0	18	0	21	0	..	27	M	Buerger's disease; syphilis (Wassermann +); sensitization to strawberries
.....	..	..	..	Casts	24.4	6.2	13.2	7.2	15	5	9.8	10	..	36	M	Probably gallbladder disease; intense pain caused by honey and pineapple
Granulations	..	..	..	Blood	21.2	7.2	9.6	8.2	12.1	0	13	0	+	18	F	Purpura hemorrhagica; sensitization to tomatoes
Granulations	+	+	..	Albumin	....	....	12.6	10.2	14.4	0	22.6	0	—	66	M	Hay-fever for years
Granulations	+	..	..	.....	18	12	8.75	0	17	0	18	0	—	67	F	Hay-fever 35 years ago; cerebral hemorrhage; urticaria
Dilatations	..	..	+	Albumin	18	8	11	10.7	27	0	30	0	—	45	M	Hay-fever every spring; alcoholism
.....	..	..	..	.....	20.4	8.6	12.4	15	10	0	22.4	0	+	52	M	Hay-fever every fall; sensitization to halibut; myocarditis; formerly dipsomania
.....	+	+	..	.....	16	8	11	0	20	0	24	0	—	58	M	Asthma; emphysema
.....	..	..	..	Albumin	20.8	14.2	11.2	18	7.4	0	7.4	0	—	43	M	Slight attack of hay-fever 45 years ago
.....	..	..	..	.....	20.4	9.8	14.2	21.4	16.4	12	20	4.8	—	39	M	Scarlet fever with kidney involvement at 4; urticaria 20 years ago
.....	..	..	..	.....	18.8	14	11.8	19.6	15.4	12.4	22.2	0	—	50	M	Angioneurotic edema when a dental student 20 years ago; alcoholism
.....	..	..	+	.....	17.2	5.8	10.8	22.4	13.4	7	21.4	7	—	44	M	Angioneurotic edema 3 years ago; dermographia
.....	..	..	..	.....	14	10.8	12.6	25	10	15.4	17	12.4	—	39	M	Grandfather had asthma; drug addict (?); urticaria 10 years ago; sensitization to sweet potatoes
Granulations	..	..	..	.....	14.8	12.4	12.4	19.2	13.4	9.2	16.2	7	—	29	M	Sugar in urine formerly; alcoholism; urticaria in 1922; tremor

tions that are constantly taking place. We have emphasized this point of view in our study of the lymph changes during shock, etc.[2]

1. Nathan, E., and Stern, F.: Klin. Wchnschr. **7**:1375, 1928.

2. Petersen, W. F.; Milles, Geo., and Müller, E. F.: Ztschr. f. Exper. Path. und Therap. **60**:336, 1928; Petersen, W. F.; Müller, E. F., and Boikan, W.: J. Inf. Dis. **41**:405, 1927.

The angioneurotic edemas and the urticarias studied seemed to be characterized by a short blister time and a relatively high inflammatory index. During an attack, the K/Ca ratio appeared to be lower. In general, the sugar level was higher. The menstrual urticaria was associated with a relative acidosis, and the reaction to epinephrine, in contradistinction to the reaction in other cases, was sympatheticotonic. Changes in the capillaries of the skin and changes in the urine were, of course, commonly associated. The intracutaneous reactions to the pharmacologic substances injected were not characteristic.

The small group of persons with gastro-intestinal sensitization all had high calcium levels and low K/Ca ratios. In two, however, distinct vascular diseases (Raynaud's and Buerger's) were associated.

Of the six persons with a history of hay-fever, three had glaucoma. Here the blood chemistry was changed so far as the K/Ca ratio was high. All were distinctly vagotonic and the capillary permeability was low in each case.

On the other hand, the persons with a history of previous angioneurotic edema and urticaria seemed to be of a somewhat different type. They were distinctly nervous and had low K/Ca ratios, but were, nevertheless, distinctly vagotonic. With two exceptions, both highly nervous persons, all showed low permeability. These two patients (nos. 77 and 80) had high resistance of the skin to electric current, high permeability of the capillaries and lessened thyroxin wheals.

The endothelial reaction of Rumpel-Leede did not seem to be characteristic for the groups.

VIII. A STUDY OF EIGHTY-THREE TUBERCULOUS PATIENTS

A. GENERAL CORRELATIONS

The study of resistance to tuberculous infection, conditioned by innumerable biologic interactions, seemingly offers insurmountable difficulties. The cellular factors, the still intangible effect of sensitization, intercellular and intracellular digestion, humoral and fixed antibodies, endocrine, vitamin, and chemical equilibriums must be considered. Add to these chance pathologic complications, constitutional inequalities, peripheral and visceral autonomic vascular and metabolic responses and emotional factors, as well as environmental influences, and one begins to shuffle some of the cards of the intricate game—all this, of course, without considering differences in the virus itself.

The organism has but two means at its disposal in overcoming the clinical disease: resorption, i.e., digestion, and its antithesis, encapsulation or insulation. Early in the disease, the former method is probably frequently successful; even in well advanced diseases, it probably plays a rôle of greater importance than is usually believed, especially in peripheral tuberculosis. But from the practical clinical standpoint, it appears that the inhibition of digestion, the suppression of inflammatory response, is of greater importance for the welfare of the patient with pulmonary tuberculosis.

Hippocratic medicine was clearly cognizant of the seasonal influence on the mortality from tuberculosis. General biologic activation in the spring, incident to environmental and intrinsic changes, is followed by dissemination of the virus. It is a condition that cannot be explained on any anatomicopathologic basis. Not only is the virus disseminated; the endothelium and other tissues of the body are receptive. This factor, as well as the analogous effect of the menstrual cycle, we discussed previously at some length.[1] Here, too, we pointed out the possible significance of changes in the status of the capillary endothelium.

In the analysis of the results of the examinations of the group of 100 so-called "normal" men (part II), we pointed out that nine gave roentgenologic evidence of active parenchymal lesions. The persons examined were workingmen; in the majority, the lesions did not present sufficient clinical manifestations to make the men aware of an unusual pulmonary disturbance. In the analysis, however, we found that this group did show a number of deviations from the "normal" (prolonged

1. Levinson, S. A., and Petersen, W. F.: Am. Rev. Tuberc. **15**:681, 1927.

TABLE 1.—*Index of the Tuberculous Patients Examined*

Patient	Age	Nationality	Advance Diagnosis;* Pulse Rate	Advance Diagnosis;* Temperature	Result of Roentgen Examination for Tuberculosis	Duration of Activity, Weeks	Condition on Examination; Weight †	Condition at Time of Writing ¶	Outcome
1	27	Jewish	M.A. A. 72- 78	98.2-98.4	Positive, not active	156	M.A. A. →	M.A. A. G. →	Discharged, living, improved
2	22	Jewish	Min. B. 60- 76	97 -98.4	R. apical healed parenchymal	20	Min. B. →	Min. B. G. →	Discharged, living, condition quiescent
3	21	Polish	Min. A. 72- 96	98.2-98.6	Negative	6	Min. →	Min. A. G. → colloid goiter	Sanitarium
4	30	American	Min. A. 68- 72	97 -98.2	Negative	208	Min. →	Min. A. G. →	Discharged, living, improved
5	20	Swedish	M.A. B. 104-120	98 -98.8	M.A.*	60	M.A. B. ↑	M.A. B. F. →	Sanitarium
6	27	German-American	Min. A. 66- 84	97 -99.4	Apical	260	Min. A. ↑	Min. A. G. ↑	Sanitarium
7	54	Norwegian	F.A. B. 72- 94	96.8-99.2	F.A.*	28	M.A. B. ↓	F.A. B. P. ↓ tuberculosis of larynx	Discharged, died
8	35	Mexican	Min. A. 76- 90	97 -98.6	Negative	26	Min. A. ↑	Min. A. G. ↑	Discharged, living, condition arrested
9	43	Polish	M.A. A. 80- 92	97.2-99	F.A.	94	M.A. A. →	M.A. A. P, → dry pleurisy and arthritis	Died
10	27	American	Min. A. 80- 92	98 -98.2	Negative	350	Min. A. →	Min. A. G. →	Discharged, living, improved
11	42	American	Min. A. 72- 80	97.6-98.6	Negative	22	Min. A. →	Min. A. G. →	Discharged, living, improved
12	37	German	M.A. A. 84- 88	97.8-99.4	F.A.	208	M.A. A. →	F.A. A. P. → cyst adenoma of thyroid, tuberculous colitis	Died, April, 1929
13	23	American	Min. B. 70- 82	97 -98.4	Negative	28	Min. B. →	Min. B. G. →	Discharged, living, improved
14	17	American	Min. B. 72- 84	97.8-98.6	Tuberculosis of hilum	16	Min. B. ↑	Min. B. G. ↑	Discharged, living, improved
15	40	Norwegian	F.A. A. 80- 92	96 -98.6	F.A.	260	F.A. A. →	F.A. A. P. → tuberculous laryngitis and enteritis	Discharged, living, not improved
16	25	Polish	Min. A. 78- 80	97 -98	Tuberculosis of hilum	572	Min. A. ↑	Min. A. G. ↑ tuberculous colitis	Discharged, living, condition arrested
17	40	German	Min. A. 76- 80	97.8-98.6	Negative	17	Min. A. →	Min. A. G. →	Discharged, living, condition quiescent
18	36	Swedish	F.A. B. 100-115	97 -102.4	Positive	260	F.A. A. ↓	F.A. A. P. ↓ Wassermann 4 plus; cavities in lung; artificial pneumothorax; spontaneous hemorrhages from lung	Died
19	54	Irish	F.A. B. 84- 88	97.4-98.6	Positive	260	F.A. A. →	F.A. A. G. → Wassermann 3 plus; syphilitic aortitis	Sanitarium
21	32	Norwegian-American	Min. A. 78-100	97 -98.8	Positive	28	Min. A. ↑	Min. A. G. ↑	Discharged, living, condition quiescent

* In diagnosis of tuberculosis, M.A. means moderate advanced at time of examination; Min., minimal or incipient, and F.A., far advanced; A., B. and C. added to these designations denote degrees of activity.

† → means weight stationary at time of examination; ↑, weight increasing; ↓, weight decreasing.

¶ In this column, G. means good prognosis at time of examination; F., fair prognosis, and P., poor prognosis.

TABLE 1.—*Index of the Tuberculous Patients Examined—Continued*

Patient	Age	Nationality	Advance Diagnosis; Pulse Rate	Advance Diagnosis; Temperature	Result of Roentgen Examination for Tuberculosis	Duration of Activity, Weeks	Condition on Examination; Weight	Condition at Time of Writing	Outcome
22	44	Dutch	M.A. A. 80- 90	98.6-98.8	F.A.	130	M.A. A. ↓	F.A. A. G. → fibroid	Sanitarium
23	22	Polish	F.A. A. 74- 80	98.6-98.6	Positive	194	F.A. A. →	F.A. A. F. →	Sanitarium
24	37	Austrian	M.A. A. 76- 84	97 -98	Positive	30	M.A. B. ↑	Min. A. G. →	Discharged, living, improved
25	25	Polish	F.A. A. 86- 88	97 -98.8	Positive	114	F.A. A. ↓	F.A. C. P. ↓ Spontaneous collapse	Died
26	21	American	M.A. A. 72- 80	98 -98.6	Positive; cavity in right apex	156	M.A. B. →	F.A. A. P. → Tuberculous enteritis	Died, March, 1929
27	43	German-American	M.A. A. 78- 90	98.4-98.6	F.A.	104	M.A. A. ↑	M.A. A. G. ↑ fibroid	Sanitarium
28	42	Bohemian	F.A. B. 72-102	97.8-101.3	F.A.	312	F.A. A. →	F.A. C. P. ↓ tuberculous enteritis and meningitis	Died
29	31	American	Min. A. 72- 90	98 -98.6	Positive	213	Min. A. →	Min. A. G. →	Discharged, living, condition arrested
30	20	Italian	M.A. A. 94-100	97 -99	Positive	104	M.A. A. →	M.A. A. G. →	Discharged, living, condition quiescent
31	21	Austrian	Min. B. 68- 72		Positive	260	Min. B. →	M.A. A. F. →	Sanitarium
32	27	Irish	F.A. A. 72- 86	97 -98.6	In apex	26	F.A. A. →	F.A. A. F. →	Discharged, living, condition arrested
33	29	Finnish	M.A. B. 90-100	98.2-98.6	F.A.	780	M.A. B. ↓	M.A. B. G. →	Discharged. living, condition quiescent
34	25	American	F.A. B. 72- 88	97.4-98.8	F.A.	104	F.A. B. →	F.A. B. P. ↓ Wassermann 4+; dermatitis exfoliativa; cavities in lungs	Discharged, died
35	40	Polish	Min. B. 70- 90	97.4-98.6	Negative	29	Min. B. →	Min. B. G. →	Discharged, living, condition quiescent
36	42	Polish	F.A. A. 80- 98	94 -100.4	F.A.	312	F.A. A. ↓	F.A. A. F. ↓	Died, November, 1928
37	17	Jewish	Min. A. 80- 84	97.2-98	Negative	828	M.A. →	Min. A. G. →	Discharged, living, condition quiescent
38	42	Norwegian	F.A. B. 74- 92	98 -98.6	F.A.	270	F.A. B. →	F.A. A. F. →	Discharged, living, condition arrested
39	45	American	M.A. B. 72- 90	97 -98.6	F.A.	156	M.A. B. ↑	M.A. B. F. ↑	Sanitarium
40	26	Bohemian	F.A. B. 74- 96	97.8-98.6	M. A.	260	F.A. B →	F.A. B. F. →	Discharged, living, condition quiescent
41	20	Jewish	F.A. B. 78-100	97.4-98.8	F.A.	78	F.A. B. →	F.A. B. F. →	Discharged, living, improved
42	29	German	F.A. B. 78- 84	97.2-98.4	F.A.	156	F.A. B. →	F.A. B. P. → tuberculous laryngitis	Sanitarium
43	20	American	M.A. B. 80- 86	97 -98.6	Positive; fluid	52	F.A. A. ↑	M.A. A. G. ↑ pleurisy; fluid	Sanitarium
44	31	Swedish	M.A. A. 74-106	98 -99.8	Positive; fluid	44	F.A. A. ↑	F.A. A. F. ↑ fluid	Discharged, living, condition arrested

TABLE 1.—*Index of the Tuberculous Patients Examined—Continued*

Patient	Age	Nationality	Advance Diagnosis; Pulse Rate	Advance Diagnosis; Temperature	Result of Roentgen Examination for Tuberculosis	Duration of Activity, Weeks	Condition on Examination; Weight	Condition at Time of Writing	Outcome
45	34	American	F.A.	B. 86-110	F.A.	104	F.A. ↑	A. F. ↑	Discharged, died
46	24	German	F.A.	B. 92-100	F.A.	130	F.A. ↑	B. F.A. G. ↑	Sanitarium; improved
47	21	Polish	F.A.	B. 100-120	F.A.	156	F.A. →	A. F.A. P. ↓	Died
48	21	Lithuanian	F.A.	A. 80- 88	F.A.	270	F.A. ↓	B. F.A. P. ↓ cavities in lungs; tuberculous laryngitis and enteritis	C. Died
49	38	German	M.A.	B. 72- 98	F.A.	70	M.A. ↑	B. M.A. P. → tuberculous enteritis	B. Discharged, died
50	21	Polish	Min.	B. 76- 80	Positive	70	Min. ↑	A. M.A. G. →	A. Sanitarium
51	30	Danish	M.A.	B. 80- 92	F.A.	64	M.A. ↓	B. F.A. F. ↑ pneumothorax; thoracoplasty	B. Sanitarium; stationary
52	19	American	F.A.	B. 76-104	Positive; fluid	52	F.A. ↑	B. M.A. F. ↑ serofibrinous pleuritis; tuberculous enteritis	A. Discharged, living, improved
53	20	German	M.A.	B. 86-120	Positive	38	M.A. →	B. M.A. P. ↓	B. Discharged, living, not improved
54	20	German	M.A.	B. 76- 94	Positive	104	M.A. ↑	B. M.A. F. ↑	A. Discharged, living, improved
55	21	Swedish	M.A.	A. 68- 88	Positive; fluid	104	M.A. ↑	B. M.A. F. ↑ fluid	B. Sanitarium
56	26	Swedish	M.A.	A. 78- 88	Positive	208	M.A. ↑	A. F.A. F. →	A. Sanitarium
57	22	Irish	M.A.	A. 62- 82	M.A.	208	M.A. ↑	M.A. G. ↑ pleurisy; arthritis	Discharged, living, improved
58	28	American	F.A.	B. 80-100	Positive	208	F.A. ↑	B. F.A. P. →	B. Sanitarium
59	20	Austrian	F.A.	B. 80- 90	Positive	156	F.A. →	B. F.A. P. → pleurisy	B. Sanitarium; fair condition
60	26	Swedish-Norwegian	M.A.	A. 88- 96	F.A.	108	F.A. ↓	C. F.A. P. ↓ cavities in lung; enteritis; colitis	C. Died
61	25	American	F.A.	C. 84- 96	F.A.; emphysema	260	F.A ↓	C. F.A. P. ↓ artificial pneumothorax; renal tuberculosis	C. Discharged, died
62	49	Irish	F.A.	A. 70- 84	Old tuberculosis; fluid	312	F.A. →	A. F.A. F. → old tuberculosis with fluid; artificial pneumothorax in 1926	A. Sanitarium; well
63	25	Bohemian	F.A.	A. 90-100	F.A.	104	F.A. ↑	C. F.A. P. ↓ phrenicotomy; thoracoplasty	C. Sanitarium
64	31	Swedish-English	F.A.	B. 80- 84	F.A.	104	F.A. ↑	B. F.A. P. ↓ multiple cavities in lung	B. Died, March, 1929

TABLE 1.—*Index of the Tuberculous Patients Examined—Continued*

Patient	Age	Nationality	Advance Diagnosis; Pulse Rate	Temperature	Result of Roentgen Examination for Tuberculosis	Duration of Activity, Weeks	Condition on Examination; Weight	Condition at Time of Writing	Outcome
65	52	German	M.A. B.	92- 98 97 -97.8	Old tuberculosis	31	M.A. A. →	M.A. A. G. →	Discharged, living, condition quiescent
66	45	Swedish	F.A. B.	88-108 96 -100	F.A.	150	F.A. B. ↓	F.A. C. P. ↓	Died
67	23	Swedish	F.A. B.	78-102 98.6-100.6	F.A.	60	F.A. B. ↑	F.A. C. P. ↓	Sanitarium; active
68	20	American	M.A. A.	92-138 98.6-103.4	F.A.	64	M.A. A. ↑	F.A. B. P. ↓	Died
69	34	German	F.A. B.	80-100 98.4-99.2	F.A.	208	F.A. B. ↑	F.A. C. P. → tuberculous laryngitis	Died
70	45	Polish	F.A. B.	82- 90 98.4-99	F.A.	468	F.A. B. →	F.A. B. F. → dry pleurisy	Died, December, 1928
71	41	American	M.A. B.	80- 82 98 -98.4	F.A.	156	M.A. B. ↑	F.A. A. F. ↑	Sanitarium
72	26	Irish	Min. B.	72- 88 97 -99	Of hilum	89	Min. B. ↑	Min. B. G. ↑	Discharged, living, condition arrested
73	43	American	M.A. B.	94- 88 97.8-99	F.A.	26	M.A. B. ↑	M.A. A. F. ↑ diabetes	Discharged, living, improved
74	45	Swedish	M.A. A.	88-108 97.2-98.6	F.A.	156	F.A. B. ↓	F.A. B. P. ↓ diabetes	Died
75	33	American	M.A. B.	92-116 97.8-100.2	F.A.	55	F.A. A. →	F.A. A. F. →	Died, living, improved
76	38	American	F.A. B.	92-122 98.4-100.4	F.A.	52	F.A. B. ↑	F.A. A. F. ↑	Died, living, condition quiescent
77	41	American	M.A. B.	67- 94 96.6-98.8	Positive	180	F.A. B. →	F.A. B. F. →	Died
78	27	Japanese	M.A. B.	88-120 98 -98.8	Positive; fluid	40	M.A. B. ↓	F.A. B. P. ↓ serofibrinous pleuritis	Discharged, died
79	17	American	M.A. A.	76- 92 97.2-98.9	M.A.	100	M.A. A. ↑	M.A. A. F. ↑	Sanitarium
80	35	American	Min. B.	68- 86 97.8-98.2	Old tuberculosis	52	Min. B. ↑	M.A. A. G. ↑	Discharged, living, condition arrested
81	25	American	F.A. B.	78- 84 97.4-99	Positive	156	F.A. A. ↓	F.A. A. F. ↓	Discharged, living, improved(?)
82	37	German	M.A. B.	80- 90 97.8-98.6	Positive	156	F.A. A. ↑	M.A. A. G. ↑	Sanitarium; condition quiescent
83	39	Slavic	M.A. B.	80- 92 97.8-99.8	F.A.	130	F.A. B. ↑	F.A. B. P. ↓	Died

blister time, decreased permeability, lowered inflammatory index, abnormal K/Ca ratio, increased globulin, increased basal metabolic rate, diminished resistance of the skin to electric current, increased muscular irritability, increased pulse rate and blood pressure, delayed reaction to ice, etc.). The members of the group were considerably older than the average and some of the changes must be ascribed to age.

Nevertheless, we deal here with a tuberculous group apparently having a chronic form of the disease with little constitutional disturbance. We must assume that these persons are relatively resistant. Certain definite deviations (chemical, vascular, nervous, etc.) appear to be associated with this status.

One of the factors is a reduction of the inflammatory response. This diminishes, in general, with progressing age, but seems accentuated in the tuberculous group. For fifty persons with an average age of 58, the inflammatory index averages 8. Our group of nine with an average age

TABLE 2.—*A Summary of the Results of the Examinations of*

Clinical Classification of Tuberculosis	Cases	Sputum, per Cent Positive	Wassermann Reaction, per Cent Positive	Tuberculosis Fixation, per Cent Positive	Daránÿi Reaction, per Cent Positive	Capillary Permeability Ratio	Blister Time, Hours	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Sugar, Mg. per 100 Cc.	CO_2 Combining Power	Cholesterol, Mg. per 100 Cc.	Lecithin, Mg. per 100 Cc.
Incipient A.....	12	0	0	16	25	63	8.6	7.6	9.1	20.8	2.27	80	53.2	186	18
Incipient B.....	7	0	0	0	43	69	7	10	10.7	18.5	1.73	77	56.4	199	17.4
Moderately active A	13	30	0	46	61	70	8.4	8.8	10.8	17.1	1.6	86	58.7	211	16.5
Moderately active B	12	50	0	58	83	67	7.4	10.4	10.2	19.6	1.92	86	59.3	192	15.6
Far advanced A...	16	69	6	87	81	70	7.2	9.9	9.8	19	1.93	83	54.5	186	15.9
Far advanced B...	18	83	11	72	72	62	6.4	9.6	10.5	19.8	1.87	88	55.1	207	15.3
Far advanced C...	5	80	0	60	100	77	11.2	6.8	10.5	18.4	1.75	89	50	192	16.9

TABLE 3.—*A Comparative Summary of the Results of the Examinations of Tuberculous*

Type of Patients in Group	Cases in Group	Blister Time, Hours	Capillary Permeability, per Cent	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Sugar, Mg. per 100 Cc.	Globulin, per Cent	Serum Protein, per Cent	Kromayer Light Erythema Time, Min.	Basal Metabolic Rate,	Resistance of Skin to Electric Current, Megohms per Sq. Cm.	Muscle Reaction, Ma.	Blood Pressure: Systolic	Blood Pressure: Diastolic	Pulse Rate
Group of 100 "Normal" Men																	
Actually normal.	20	6.7	63	9.4	10.2	20.6	2.05	71	33	8.04	130	+7.5	0.37	3.2	115	68	66
Showing healed parenchymal tuberculosis.....	12	7.3	65	9	10.3	20.3	1.97	73	24	7.88	120	+7	0.32	3.6	115	68	78
Showing active parenchymal tuberculosis, roentgenologically....	9	8.4	59	7	9.6	20.1	2.08	70	41.7	8.08	114	+18.2	0.28	2.2	133	73	78
Group of Patients in Sanitarium																	
Gaining weight...	36	7.2	65.3	9.5	10.6	18.9	1.80	85	33	8.75	90	+7.4	....	...	121	73	82
Stationary.....	32	7.6	66.2	8.6	10.4	20.1	1.96	84.7	27	8.55	91	+8	....	...	121	70	88
Losing weight....	13	7.7	69.6	9.7	10.2	17.7	1.73	86.6	43	9.03	79	+8.4	....	...	112	72	91

of 58.7 has an index of 7.5. The slowing of the reaction to ice is in line with the expectancy from the age of the group (column 19, table 1, part I.).

The diminution of the inflammatory response has taken place despite an increase in the basal metabolic rate, and the weight length ratio gives evidence that no serious inroad has been made so far as the general well being of the group is concerned.

Apart from the definite increase in the basal metabolic rate, the increase in globulins, the definite disturbance of the K/Ca ratio, the increase in the pulse rate, etc., offer evidence of the activity of the disease.

Tuberculous Persons Correlated on the Basis of Clinical Classifications

Corpuscles/Plasma Ratio	Kromayer Light Erythema Time, Min.	Complexion	Endothelial Reaction, per Cent Positive	Reaction to Ice, Seconds	Capillaries, per Cent Pathologic	Basal Metabolic Rate	Urine, per Cent Pathologic	Influenza, per Cent Positive	Leukocyte Count	Pulse Rate	Blood Pressure		NaCl Test (McClure–Aldrich), Min.	Reaction to Tuberculin, Mm.		
											Systolic	Diastolic		24 Hours	48 Hours	72 Hours
43.00/57	84	5	41	13	0	+1.7	0	66	9,700	83	121	71	72	6	6.7	3.2
38.00/62	100	5	28	16	0	+0.8	14	43	11,800	77	109	65	70	7.8	9	5
41.60/58.4	94	4.4	38	10.4	0	+9.2	0	38	11,900	86	120	72	75	7.4	4.1	2.4
39.25/60.75	100	4.5	33	13	0	+3.4	0	50	13,008	89	117	72	78	9	4	1.6
40.00/60	90	4.3	44	11.5	6	+7.4	31	44	13,000	89	119	70	85	8	8	5
36.30/63.7	85	4.2	39	10.3	5	+14	22	44	13,300	97	118	70	75	8.4	7	4.5
39.30/60.7	97	2.8	40	11.8	20	+15	40	20	10,500	104	113	75	93	8.6	9	4.8

Persons and of "Normal" Persons on the Basis of the Weight Curves

Reaction to Epinephrine		CO_2 Combining Power	Reaction to Ice, Seconds	Age	Weight/Length Ratio	Cholesterol, Mg. per 100 Cc.	Lecithin, Mg. per 100 Cc.	Sputum, per Cent Positive	Tuberculosis Fixation, per Cent Positive	Darányi Reaction, per Cent Positive	Endothelial Reaction, per Cent Positive	Leukocyte Count	Increase in Leukocyte Count after Intracutaneous Injection of Aolin, per Cent	Corpuscles/Plasma Ratio	Tuberculin Reaction, Mm.			NaCl Test (McClure–Aldrich), Min.
Pulse Pressure, per Cent	Pulse Pressure × Pulse Rate, per Cent														24 Hours	48 Hours	72 Hours	
15	21.6	56	14.7	38.3	229	211	....	..	..	..	..	. ....	..	.....	...	...	...	..
21	26	57.1	16.8	42	221	226	....	..	..	..	..	.....	..	.....	...	...	...	..
11	23	58.8	21	58.7	215	208	....	..	..	..	..	.....	..	.....	...	...	...	..
—5	—5	57.5	12	28.6	195	199	16.3	43	60	73	43	10,680	5	38.2/61.8	8	7	4.7	85
—4	0	55.3	12	32.7	197	200	16.7	46	46	60	37	12,900	4	40.8/59.2	8.1	7.1	3.4	77
—5	—5	55.8	10	33.2	180	198.3	15.4	77	61	70	30	11,400	1	40.5/59.5	7	4.8	2	62

In order to investigate further some of the interrelations of the resistance and the chemical status of these persons, we made a study of eighty-three patients of the Municipal Tuberculosis Sanitarium. The patients (all men) in various stages of clinical activity and progression were selected so as to give us a fair cross-section. In table 1 are recorded the serial number of each patient, his age, his clinical status, the x-ray diagnosis and the complications.

ANALYSIS ON THE BASIS OF THE CLINICAL CLASSIFICATION

In table 2, we present summaries of the results of the examinations of the patients with tuberculosis when arranged on the basis of clinical classifications. It is unnecessary to point out that an analysis on such a basis affords little insight into any actual correlation between resistance and the chemical and autonomic status of the patient. A case of far advanced tuberculosis may be one that is chronic, and associated with

TABLE 4.—*Results of Examinations of Patients Who Were in Good*

Patient	Diagnosis	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Erythema Time, Min.	Reaction to Ice, Seconds	CO_2 Combining Power
55	M.A. B.	6.5	82	12.6	12.9	21.5	1.66	40	10.7	100	10	61.2
16	Min. A.	13	69	5.3	....	....	....	26	8.16	60	12	51.4
6	Min. A.	6	56.1	9.3	9.4	14.2	1.5	17	8.77	20	12	56.8
21	Min. A.	7	64.1	9.5	8.8	19.4	2.2	30	6.98	110	16	58.5
80	Min. B.	6.5	64	9.8	9.97	19	1.9	12	7.91	...	12	51.8
79	M.A. A.	9	67.2	7.4	11.5	17.5	1.5	20	8.94	...	18	55.5
39	M.A. B.	10.5	69.4	6.1	9.3	16.3	1.75	26	7.73	175	10	56.9
27	M.A. A.	9	51.9	5.7	13.1	15.2	1.16	22	9.64	140	7	58
43	F.A. A.	6	69.2	11.5	....	....	....	3	6.71	60	5	56.8
46	F.A. B.	6	72.8	12.1	9.9	22.5	2.27	42	9.35	90	12	55
44	F.A. A.	7	80.9	11.5	....	....	....	32	7.41	78	5	48.4
45*	F.A. A.	7	65.1	8.6	11.8	20.6	1.74	40	9.45	100	20	56.9
76	F.A. B.	6.5	70.9	10.9	12.5	19.45	1.55	65	9.87	...	15	60.9
82	F.A. A.	8	61.3	7.6	9.4	17.7	1.87	25	12	...	12	49.4
52	F.A. B.	6	57	9.5	9.6	19.3	2.1	100	11.5	75	2	....
71	M.A. B.	6	75.9	12.6	12.2	19.1	1.57	38	7.63	...	17	64
16	Averages....	7.5	67.3	9.37	10.7	18.5	1.75	33	8.92	91.6	11.5	56.1

* Died, 1929.

relatively high resistance; a case of minimal manifestation of the disease, one that may go on to death in a relatively short time.

When we examine these averages, we find no consistency. While the permeability of the capillaries of the skin ranges from 63 in the patients with the minimal manifestations to 77 in the patients with the far advanced conditions, the intermediary groups show no progressive relation. In general, calicum increases; but here, too, there is no consistent progression. Potassium diminishes, as do lecithin and the CO_2 combining power, but all the averages are irregular. As is to be expected, the Darányi reaction, the globulins, the complement fixation and the basal metabolic rate increase in fairly consistent fashion.

ANALYSIS ON THE BASIS OF THE WEIGHT CURVE

The analysis based on the weight curve of the patient might offer a better approach and in table 3 we present such a summary. Two patients of the series are not included because of the briefness of the period of observation at the sanitarium. For purposes of comparison, we present first the averages for the truly normal persons, those showing roentgen evidence of "healed" tuberculosis and those showing roentgen evidence of "active" tuberculosis of our series of 100 "normal" men.

Condition When Examined and Who Improved During the Two Years Following

Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure-Aldrich), Min.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
							24 Hours	48 Hours	72 Hours		
Vagotonic	18	14	7	8	1.6	85	17	5	5	—	38.2
Sympathetic-cotonic	15	2.1	3	0	1.12	80	0	0	0	—	36.3
Vagotonic	15	6.7	10	7.5	1.02	80	8	10	0	—	40.5
Vagotonic	17	8.7	4	0.5	0.94	77	5	4	4	+	42.8
Sympathetic-cotonic	18.7	7.8	10	2.5	1.32	60	12	12	12	—	34.2
Sympathetic-cotonic	12.2	6.3	10	2.5	1.77	70	5	4	4	++++	32.4
Vagotonic	13.5	7.6	10	2	1.53	95	20	6	0	A.C. ?	38.4
Vagotonic	15.2	2.8	8	1.5	1.38	77	8	6	0	++	52.05
Vagotonic	14.5	11.7	6	2	1.38	120	12	25	25	+	35.7
Vagotonic	18	12.6	10	0	1.3	60	5	10	14	++	26.8
Vagotonic	16.2	8.7	12	0	1.51	105	8	15	14	++	45
Vagotonic	16.5	9.7	10	10	1.41	62	9	11	13	++++	32.9
Sympathetic-cotonic	10	11.6	10	0	....	75	8	8	8	++	35.4
Vagotonic	16	4.7	12	0	1.15	120	8	6	4	+	34.6
Vagotonic	13.7	17	10	10	1.5	115	10	3	3	+++	46.5
Sympathetic-cotonic	17	3.7	12	0	....	75	5	5	3	+	....
11 V., 5 S.	15.4	8.4	9	1.7	1.35	84.7	8.7	8.1	6.8	4 —, 11 +, 1 A.C.	38.7

When we examine the averages for the tuberculous patients, we apparently approach certain correlations of significance. It will be observed that the permeability of the capillaries increases and the blood calcium diminishes (as does the K/Ca ratio). The Kromayer light erythema time, the ice reaction time and the NaCl test (McClure-Aldrich) time are lessened, as we pass from the gaining to the losing groups. In a previously published analysis,[2] we showed the differences in the curves of the blood pressure following the injection of epinephrine and the change in the leukocyte count following injections of a non-specific milk preparation in these groups of patients. These curves

2. Petersen, W. F., and Levinson, S. A.: Am. Rev. Tuberc. **18**:616 and 839, 1928.

TABLE 5.—*Results of Examinations of Patients Who Were*

Patient	Diagnosis	Weight	Condition at Time of Writing	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent
53	M.A. B.	Stationary	Losing	6	71.5	11.5	12.9	24	1.85	45	8.8
63	F.A. C.	Gaining	Losing	7	82	11.7	10.2	17.2	1.68	36	9.9
69	F.A. B.	Gaining	Dead	6	67	11.1	10	13.9	1.39	60	9.35
49	M.A. B.	Gaining	Dead	7.5	44	5.8	8.6	22.4	2.6	40	9.9
83	F.A. B.	Gaining	Dead	6	74.7	12.4	13.1	21.6	1.65	26	8.67
67	F.A. B.	Gaining	Losing	6	58	9.6	11.6	19.2	1.65	60	10.7
64	F.A. B.	Gaining	Dead	6	56.4	9.4	12	19	1.59	30	10.6
68	M.A. A.	Gaining	Dead	9	32	3.5	10.6	14.3	1.35	20	8.06
34	F.A. B.	Stationary	Dead	7	42	6.1	9	19.1	2.13	28	8.6
58	F.A. B.	Gaining	Stationary	7	45	6.4	11	17.4	1.57	17	11
56	M.A. A.	Gaining	Stationary	8	67	8.3	8.6	18.1	2.1	15	7.79
	Averages.....			6.8	58.1	8.7	10.6	18.7	1.77	34.2	9.39

TABLE 6.—*Results of Examinations of Tuberculous Patients*

Patient	Diagnosis	Condition at Time of Examination	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Erythema Time, Min.
37	M.A. A.	Arrested	9	60.7	6.7	11.4	23.7	2.08	10	8.7	33
41	F.A. B.	Improved	7.5	78	10.4	....	....	....	34	7.85	147
75	F.A. A.	Improved	6	62.3	10.3	10.3	17.6	1.71	100	9.33	...
77*	F.A. B.	.....	6	43	7.1	10.8	21.6	1.98	5	12.9	...
73	M.A. B.	Improved	6	63.1	10.5	11.6	17.6	1.53	35	9.35	...
65	M.A. A.	Quiescent	..	....	....	12.2	23.8	1.95	23	9.56	110
42	F.A. B.	.....	6	65	10.9	9.5	16.6	1.75	50	10.4	60
62	F.A. A.	Well	6	69	11.5	8.2	14.4	1.75	7	7.73	85
70	F.A. B.	Stationary	6	37.7	6.2	13.4	23.9	1.79	45	11.27	...
59	F.A. B.	.....	6	68.4	11.4	....	....	....	15	9.35	190
19	F.A. A.	Wassermann ++	8	56	8.3	8.8	18.9	2.15	22	7.98	50
30	M.A. A.	Quiescent	6	88	14.6	10.8	17	1.57	40	7.91	170
23	F.A. A.	.....	8	76	9.5	9.5	23.1	2.43	30	8.56	140
24	M.A. B.	Quiescent	8.5	72	8.4	8.4	24.5	2.92	10	7.85	80
32	F.A. A.	Arrested	7	72.1	10.3	9.5	15.6	1.64	25	8.28	142
40	F.A. B.	Quiescent	7.5	69.3	9.2	8.8	22.4	2.55	45	6.43	70
38	F.A. B.	Arrested	7	65.6	9.3	9.3	26.8	2.88	10	8.06	130
29	Min. A.	Arrested	9	60.7	6.7	11	18.6	1.69	25	8.7	237
1	M.A. A.	Improved	8	74	9.3	10.2	15.2	1.51	5	7.63	45
5	M.A. B.	Stationary	8.5	75	8.8	9.1	15.4	1.69	32	8.5	90
	Averages.....		7.1	66.4	9.44	10.1	19.8	1.97	28.4	8.817	111

* Died, 1929

Doing Well When Examined but Who Subsequently Grew Worse

Kromayer Light Erythema Time, Min.	Reaction to Ice, Seconds	CO_2 Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure-Aldrich), Min.	Reaction to Tuberculin, Mm. 24 Hours	48 Hours	72 Hours	Tuberculosis Fixation	Corpuscles/Plasma
120	15	51.9	Vagotonic	15.7	7	12	0	1.30	90	7	3	4	+++	38.4
85	12	53.5	Vagotonic	14.2	6.7	12	0	1.21	130	10	10	0	—	44.3
25	10	59.8	Sympathetic-cotonic	13	4.2	9	3.5	1.16	35	6	5	4	+++	37.1
78	19	57.3	Vagotonic	7.2	8	10	2.5	1.04	85	10	9	0	+++	35.5
..	8	56.3	Vagotonic	20.7	6.5	10	4	....	45	21	12	8	—	32.1
40	23	58.9	Sympathetic-cotonic	16.5	10.1	12	1	1.05	30	4	4	6	++++	34.6
65	15	56.3	Sympathetic-cotonic	17.7	8.1	10	5	1.23	90	11	3	2	++++	38.2
110	15	55.4	Sympathetic-cotonic	8	4.7	14	0	1.22	110	8	8	6	—	38.1
71	1	62.7	Sympathetic-cotonic	13.7	6.6	10	9	1.62	85	8	0	0	+++	42.9
65	6	65	Vagotonic	16	4.5	12	0	1.4	159	7	15	8	—	19
85	10	59.4	Vagotonic	10.7	8.2	12	0	1.32	120	10	6	6	++++	48.8
74.4	12.1	57.8	6 V., 5 S,	13.9	6.7	11.1	2.27	1.25	89	9.2	6.8	4	7 +, 4 —	37

in Whom Disease Was Stationary and Remained So

Reaction to Ice, Seconds	CO_2 Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure-Aldrich), Min.	Reaction to Tuberculin, Mm. 24 Hours	48 Hours	72 Hours	Tuberculosis Fixation	Corpuscles/Plasma
7	58.7	Vagotonic	16.7	9.5	7	1.5	1.25	85	2	5	8	—	43.2
12	49.8	Vagotonic	15.5	6.6	6	5	1.53	85	10	25	8	—	37.5
18	53.5	Sympathetic-cotonic	10.75	7.25	6	0	1.30	145	28	12	6	++++	34.3
25	55.4	Vagotonic	11.5	5	14	0	1.35	83	11	8	6	++++	31.1
15	59.3	Vagotonic	18.25	5.75	13	1.5	1.15	60	6	8	4	+++	36.05
12	....	Vagotonic	11.7	5.7	7	0	1.38	85	8	5	3	+	45.1
20	63.8	Vagotonic	17.5	11.8	7	14	1.73	75	22	10	3	—	46.7
30	47.9	Vagotonic	17.5	4.75	15	0	1.07	85	12	22	0	+++	54.2
3	52.9	Vagotonic	5.2	3.1	6	0	1.03	68	6	7	8	++	40.1
10	53.7	Sympathetic-cotonic	7.5	3.1	11	2	1.3	80	5	10	0	—	29
12	54.4	Vagotonic	19.2	6.6	5	10	0.92	92	7	7	0	+	44.5
15	51.4	Sympathetic-cotonic	25.5	10.2	10	0	1.05	..	14	3	0	—	36.4
8	68	Sympathetic-cotonic	12.5	6.3	5	1.5	1	40	3	3	0	++++	41.3
5	66	Sympathetic-cotonic	15.5	6.6	9	3	1.09	190	5	0	0	—	41.1
12	43.9	Vagotonic	18.5	8	20	5	0.98	..	3	0	0	—	47.1
8	56.9	Vagotonic	17	5.8	10	5	1.84	35	0	0	0	++	43.1
5	57.2	Vagotonic	23.7	9.5	10	12.5	1.43	80	0	0	0	+	35.1
8	40.1	Vagotonic	14	6.75	4	3	0.95	65	10	6	7	—	51.1
15	58.6	Vagotonic	17.5	6.5	9	0	1.06	..	0	0	0	—	42
15	57.2	Vagotonic	7.7	3	6	0	1.05	70	20	0	..	—	45.2
12.7	55.1	15 V., 5 S.	15.16	6.59	9	3.2	1.223	83.7	8.6	6.5	2.6	10 +, 9 —	41.2

showed a consistent increase in the vagotonic effect in the losing groups. The mathematical calculation of the pulse pressure following the injection of epinephrine shown in table 3 merely indicates the decided difference existing between the actively tuberculous groups and the

TABLE 7.—*Results of Examinations of Tuberculous Patients Who*

Patient	Diagnosis	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Erythema Time, Min.	Reaction to Ice, Seconds	CO_2 Combining Power
22	M.A. A.	7.5	81.7	10.8	9.5	22.1	2.33	29	7.1	18	2	74
33	M.A. B.	8	62	7.7	10	16.3	1.63	25	7.8	75	15	53.7
36*	F.A. A.	6	76	12.6	9.9	26.2	2.67	43	8.9	111	12	55.3
51	M.A. B.	5.1	68.5	9.7	9.9	20.3	2.05	80	10.5	90	8	66.8
	Averages.....	6.6	72	10.4	9.8	21.2	2.17	44.2	8.5	73.5	9.2	62.4

* Died, November, 1928.

TABLE 8.—*Results of Examinations of Tuberculous Patients*

Patient	Diagnosis	Condition at Time of Writing	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Protein, per Cent	Kromayer Light Erythema Time, Min.	Reaction to Ice, Seconds
9	M.A. A.	Dead	8	72.4	8.04	10.2	19.1	1.87	9	8.28	15	2
18	F.A. A.	Dead	8	75	9.4	8.4	21.7	2.58	75	8.8	10	3
61	F.A. C.	Dead	6	69	11.5	10.5	18.8	1.79	43	10.2	30	10
47	F.A. A.	Dead	6.4	73	11.2	10.9	20.3	1.85	28	9.45	105	12
66	F.A. C.	Dead	8	82	11.5	10.2	19.6	1.92	80	9.66	95	16
60	F.A. C.	Dead	7.5	79	10.5	11.1	19.2	1.73	48	8.70	90	20
78	M.A. B.	Dead	7	73	10.7	10.4	19.2	1.84	15	9.87	...	13
48	M.A. B.	Dead	7.5	62.5	8.2	8.5	16.2	1.91	40	9.92	115	8
74	F.A. B.	Dead	6	58	9.6	10.1	17.9	1.72	46	8.06	...	5
28	F.A. A.	Dead	7	75	10.7	....	....	....	50	8.92	163	9
25	F.A. A.	Dead	8	74	9.3	9.9	15.4	1.56	67	7.73	93	12
7	M.A. B.	Dead	8.5	71	8.3	9	14.3	1.59	31	7.36	8	5
15	F.A. A.	Stationary	8	75	9.3	9.7	19.4	2	32	8.36	40	4
26	M.A. B.	Dead	4.5	70	15.4	11.4	17.3	1.52	35	8.28	193	20
31	Min. B.	Stationary	7	74.2	10.6	12.8	15.7	1.23	42	9.02	156	8
	Averages		7.1	72.2	10.2	10.2	18.1	1.79	42.7	8.84	85.6	9.8

group of "normal" persons, the group of persons with "healed" lesions and the group with roentgen evidence of "active" tuberculosis.

On the other hand, the values for globulin follow more consistently the clinical classification, as do those for the Darányi reaction, the complement fixation, the basal metabolic rate, etc.

While the analysis based on the weight curve enables us to reach certain definite conclusions, the weight curve alone is by no means a

criterion of resistance. Apart from the fact that periodic fluctuations may depend solely on fluctuation of the water balance, patients may be gaining at the time of the examination and shortly afterward present a reversal.

Were Losing Weight and Who Subsequently Showed Improvement

Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure-Aldrich), Min.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
							24 Hours	48 Hours	72 Hours		
Vagotonic	15	8.6	6	2.5	1.06	45	8	12	0	++	32.6
Sympatheticotonic	11.5	6.75	8	2	1.6	93	11	0	0	—	39.1
Sympatheticotonic	16.2	6	10	5	....	95	2	4	0	++++	46.5
Sympatheticotonic	11.5	6.1	10	11.5	1.64	95	12	4	0	++++	40.7
3 S., 1 V.	13.5	6.8	8.5	5.25	1.43	82	8.2	5	0	3 +, 1 —	39.7

Who Were in Poor Condition and Who Grew Worse

CO_2 Combining Power	Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure-Aldrich), Min.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
								24 Hours	48 Hours	72 Hours		
62.1	Vagotonic	18	5	6	4.5	1.18	75	0	0	0	—	46
55.1	Sympathetic-otonic	17	6.8	5	4	1.05	45	6	7	10	+	34.5
42.5	Sympathetic-otonic	15.7	4.7	7	0	1.31	75	5	6	8	+++	45.5
55.2	Vagotonic	10.5	6.3	8	18.5	1.2	105	7	7	7	+	40.7
53.5	Vagotonic	12	8.7	12	0	0.94	75	9	9	7	++	34.3
38.8	Vagotonic	15.2	5.5	10	0	1.18	65	7	5	3	—	51.1
57.5	Sympathetic-otonic	12.5	6	10	1	1.33	18	8	6	3	—	37.1
57.2	Vagotonic	15.2	13	9	11	1.65	90	8	4	3	++++	44.1
60.3	Vagotonic	15	5.7	14	0	1.24	48	9	3	0	+	34.8
59.2	Vagotonic	23.5	5.3	8	0	1.1	80	7	3	0	+++	36
51.8	Vagotonic	12.7	5.6	10	5.5	1	87	7	0	0	+++	30.9
57.2	Vagotonic	17	5.7	4	5.5	1.13	40	5	0	0	—	37.3
62.5	Vagotonic	20.5	6	9	2.5	1.12	50	0	0	0	—	37.7
57.2	Vagotonic	11.25	5.7	5	7.5	1.17	52	4	0	0	+++	38
57.2	Vagotonic	14.5	5.37	10	5	1.05	15	5	0	0	—	46.1
55.1	12 V., 3 S.	15.37	6.35	8.4	4.3	1.17	61.3	5.8	3.3	2.7	9 +, 6 —	39.6

SUMMARY BASED ON PROGNOSIS

The patients of the series studied were examined during the summer of 1927. As all were sanitarium patients, it was possible to follow the clinical course of the disease in each and to analyze the results of the examinations on the basis of the condition in 1929. In tables 4 to 8, we present the results of the more important examinations of these patients when so classified.

When we examine the summaries in table 9 certain deductions appear warranted.

Lower Capillary Permeability in Patients with Good Prognosis.—While occasionally increased permeability is found in persons of this type (no. 44 and 55 in the group who were gaining—both, however, with pleuritic effusion), generally, as we showed previously, it goes hand in hand with progression of the disease, while persons with silent lesions (the ones with roentgen evidence of active tuberculosis in the series of 100 "normal" men) have low permeability.

TABLE 9.—*A Summary of the Results of Examinations*

Table	Number in Group	Condition at Time of Examination	Blister Time, Hours	Permeability Ratio	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent
4	16	Good; continued improvement....	7.5	67.3	9.3	10.7	18.5	1.75	33
5	11	Good; later poor.....	6.8	58.1	8.7	10.6	18.7	1.77	34
6	20	Stationary.....	7.1	66	9.4	9.1	19.8	1.97	38
7	4	Poor; later improved.....	6.6	72	10.4	9.8	21	2.17	44
8	15	Poor; continued extension.....	7.1	72	10.2	10.2	18.1	1.79	42.7

For many reasons, a question of utmost importance immediately comes up. Is the increased capillary permeability that is associated with poor prognosis and progression of the disease due to the clinical condition or does the increased permeability bring about the progression? If the former, we deal merely with an incident of clinical observation; if the latter, we have at our command an approach to one of the factors in therapeutic control. This is discussed in article VIII C, p. 236. The clinical association is obviously close. In the group who were doing well when first examined and who later showed decline (table 5), the capillary permeability was low. In the group who were doing poorly when first examined and who showed subsequent improvement (table 7) capillary permeability was high.

The status of the capillary wall—the functional capacity—is obviously a most labile affair, depending not only on the activity of the

local tissue, but on endocrine (probably thyroid-suprarenal-pituitary) and chemical equilibriums, as well as on autonomic disturbances. With so many variable factors, one cannot assume any dogmatic position. Certainly, acute intoxications increase the capillary permeability.[3] Presumably, tuberculin may diminish as well as increase it.[4] Progression of the disease might logically be expected to increase permeability. On the other hand, there is evidence to support the view that the status of the capillary may be the predetermining factor on which either fixation or dissemination depends. We have mentioned the relation to

of Tuberculous Patients (Tables 4 to 8)

Vascular Reaction to Epinephrine	Epinephrine, Wheal, Diameter, Mm.	Epinephrine, Flare, Radius, Mm.	Thyroxin, Wheal, Mm.	Thyroxin, Flare, Mm.	Cholesterol/Lecithin	NaCl Test (McClure-Aldrich), Min.	Reaction to Tuberculin, Mm.			Tuberculosis Fixation	Corpuscles/Plasma
							24 Hours	48 Hours	72 Hours		
11 Vagotonic / 5 Sympatheticotonic = 30%	15.4	8.4	9	2.6	1.35	84.7	8.7	8.1	6.8	70	38.7
6 Vagotonic / 5 Sympatheticotonic = 45%	13.7	6.7	6.7	2.2	1.25	89	9.2	6.8	4	63	37
15 Vagotonic / 5 Sympatheticotonic = 25%	15.1	6.6	9	3.2	1.22	83.7	8.6	6.5	2.6	52	41.2
1 Vagotonic / 3 Sympatheticotonic = 75%	13.5	6.8	8.5	3.2	1.43	82	8.2	5	0	75	39.7
12 Vagotonic / 3 Sympatheticotonic = 20%	15.3	6.3	8.4	4.3	1.17	61.3	5.8	3.3	2.7	60	39.6

season. A similar case may be made out for the menstrual cycle, for remote trauma and for inanition. But, again, we must not forget that in thyroid disease, with its accompaniment of greatly increased permeability, no direct relation to activation of tuberculosis exists.

Lowered Inflammatory Index in Cases with a Favorable Prognosis.—While the differences are not great, the grouping shows conclusively that the inflammatory response of the skin in patients doing well is seemingly diminished. In the introductory paragraphs, we presented our reasons for believing that such a lowering of the inflammatory response may be of benefit to the patient in protecting him from too

3. Petersen, W. F.: Permeability of Skin Capillaries in Various Clinical Conditions, Arch. Int. Med. **39**:19 (Jan.) 1927.

4. Petersen, W. F., and Levinson, S. A.: Am. Rev. Tuberc. **8**:122, 1923; J. Immunol. **8**:387, 1924.

great an absorption of toxic material. Many coordinated problems enter into consideration, because certain types of tuberculous lesions may be observed in which inflammatory response may be most useful (skin, etc.). Generally speaking, the clinician has tried to build up a resistance to inflammatory response, either by immunizing his patient until the reaction of the skin has diminished in intensity or by using nonspecific methods to bring about the same result. The therapeutic goal in common practice is distinctly inhibitory, even when brought about by the methods which may transiently accelerate the inflammatory response.

High Blood Calcium Level in Cases with Good Prognosis.—The explanation of the calcium values is, we believe, relatively simple. The cases with good prognosis have a high level; with progression this declines. In cases that have a poor prognosis, calcium is evidently swept into the serum from the tissues and raises the level in the serum. It will be seen that there is no relation of the calcium level to the clinical status when the results of the examinations of the patients are arranged on the basis of the classification made by the National Tuberculosis Association. When the results are arranged on the basis of the weight curve, the patients who are gaining show a higher calcium level. There appears to be no necessary relation to the K/Ca ratio.

High Serum Globulin in Cases with Poor Prognosis.—As an index of activity, the increase in globulin—and with it a coincident increase in the degree of positiveness in such a reaction as the Darányi reaction—is, as might be expected, clearcut. The concentration of serum protein, is, on the other hand, not particularly characteristic.

Apparently Sympatheticotonic Reactions to Epinephrine.—In a previous study of the curves of the reactions of these patients to epinephrine, we called attention to the fact that when the results are grouped on the basis of the weight curve, the patients who are gaining are shown to have a less marked vagotonic reaction than those have who are losing. In the tables here presented, we have merely indicated the general character of the curves by designating those as sympatheticotonic in which a primary increase in the systolic blood pressure can be ascertained in the first fifteen minutes after a subcutaneous injection of epinephrine hydrochloride.

In our series of 100 "normal" men, approximately 40 per cent give a distinctly sympatheticotonic reaction.[5] In the tuberculous group, 32 per cent were so classified. But when we estimate effects on the basis of the actual increase in pulse pressure, the 100 "normal" men show an average increase of approximately 14 per cent during the hour after

5. Relation of Reaction to Epinephrine to Potassium/Calcium Ratio and to Other Ratios, p. 121. Article VIII D, A Study of the Reaction to Epinephrine in Tuberculous Patients, p. 260.

the injection, while the tuberculous persons show an actual loss of 5 per cent.

In general, it appears that there are more sympatheticotonic reactions among the patients with favorable prognoses. We desire, however, that this conclusion be regarded with reservation. The reactions to epinephrine by no means conform to the fixed or rigid outlines formerly accepted. When one examines the individual curves, one is rather struck by the irregularity in the tuberculous person as compared with the "normal" person. We believe that this is an expression of the general autonomic instability. In the series of four patients who were losing and who later improved (table 7) there is an observation that may be of some significance. Of the four, three had a distinctly sympatheticotonic reaction. Whether this presaged the later favorable development we do not know.

The Bearing of the Intracutaneous Reactions. — Of the intracutaneous reactions, only the flare due to the injection of thyroxin seems to be of interest. The persons with favorable prognoses appear to be less reactive. This may be in line with the general diminution of the inflammatory reaction; it may be related to the same phenomena that underlie the delay in their reaction to ice and the lessened permeability of their capillaries (see table 1 part I).

Larger Value for the Cholesterol/Lecithin Ratio in Persons with Favorable Prognoses.—A distinct correlation exists between the clinical condition and the cholesterol/lecithin ratio, an exception being found only in the group shown in table 7. Here a high value of the ratio existed with a declining weight curve at the time of examination. Just as with the reaction to epinephrine the possibility exists that this reaction is of some prognostic significance. The assumption that the outcome of the reaction to epinephrine may depend on the cholesterol/lecithin ratio is unfounded. Our sympatheticotonic patients show both high and low values for this ratio.

Shortening of the McClure-Aldrich Sodium Chloride Disappearance Time in the Cases with "Poor" Prognosis.—This is apparent in the tables in which the results are arranged in accordance with the weight curve, as well as in the final arrangement on the basis of prognosis. On the other hand, the fallacy inherent when only the N. T. A. clinical classifications are used becomes apparent when we study table 1. Here the far advanced "C" cases (five in number) have an average disappearance time of 93 minutes, i.e., longer than that of any of the other groups. However, the three members of this group who died had a 75 minute disappearance time, while the two still living had a prolonged time of 130 and 110 minutes, respectively. The average, of course, gives an entirely wrong impression. It would appear that the reaction might serve a useful purpose in the prognosis.

Cases with Favorable Prognosis Characterized by a More Marked Reaction to Tuberculin.—Both in the size of the wheal and in the persistence of the infiltration, the patients with the favorable prognoses reveal a considerable accentuation. On the other hand, there is no characteristic difference in the circulating antibodies (complement fixation) nor any striking difference in the corpuscle/plasma ratio.

ANALYSIS OF RESULTS IN FATAL CASES

Finally, we present an analysis of the results of the examinations in cases that have terminated fatally. During the twenty months that elapsed between the time of the examination and the time of this analysis,

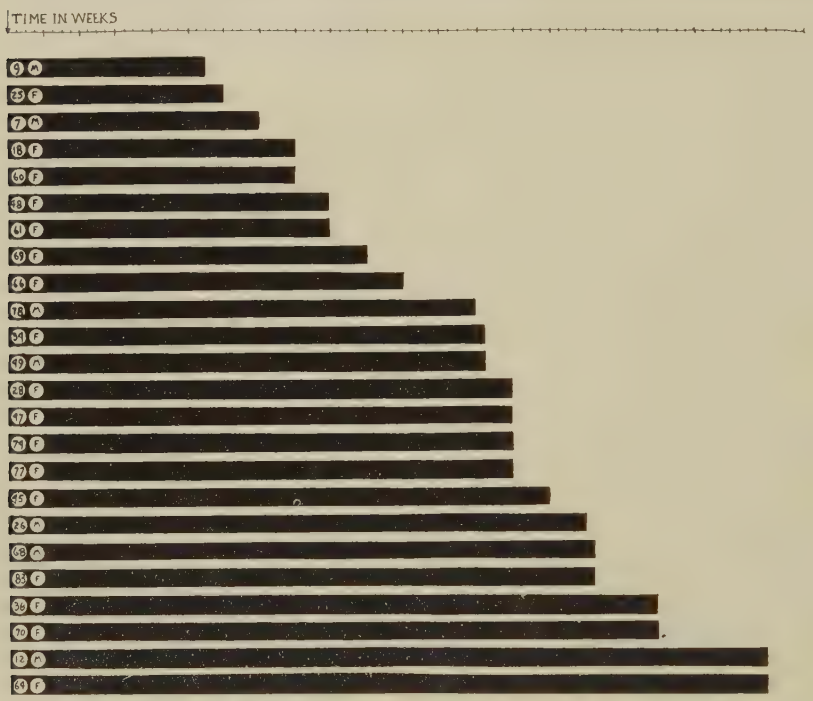

Chart 1.—Fatal cases: The duration of the illness from the time of examination to the time of death (in weeks). *F* means far advanced; *M*, moderately advanced. The numbers are the case numbers.

twenty-four patients died either in the hospital or elsewhere in the city. Two with far advanced tuberculosis left the city and they probably died, but we have not included them in the group.

In the chart the duration of life after the time of the examination is indicated by the length of the column. The number of the patient and the type of the case at the time of the examination (*F*, far advanced; *M*, moderately advanced) are noted in the circles.

In table 10, the more interesting data have been collected. An average has been made for the twelve patients living for the shorter periods

to be contrasted with that for the group of twelve who died later. The total period of clinical activity until the time of death averaged 45 months for the former group and 65 months for the second group.

An examination of the table indicates the following: The first group, the short lived ones, had the more permeable capillaries (67 as compared

TABLE 10.—*Results of Examinations of Patients with Fatal Tuberculosis, One Group Short Lived and the Second Group Longer Lived*

Patient	Total Time of Activity Until Death, Mo.	Capillary Permeability	Calcium, Mg. per 100 Cc.	Potassium, Mg. per 100 Cc.	K / Ca Ratio	Globulin, per Cent	Cholesterol, Mg. per 100 Cc.	Lecithin, Mg. per 100 Cc.	Reaction to Tuberculin			NaCl Test (McClure-Aldrich), Min.	Reaction to Ice, Seconds	Reaction to Epinephrine
									24 Hours	48 Hours	72 Hours			
9	29	72	10.2	19.1	1.87	9	208	17.5	0	0	0	75	2	Vagotonic
25	35	74	9.9	15.4	1.56	67	171	17.1	7	..	..	87	12	Vagotonic
7	14	71	9	14.3	1.59	31	190	16.7	5	..	..	40	5	Vagotonic
18	13	75	8.4	21.7	2.58	75	167	15.8	6	7	10	45	3	Sympathetic-otonic
60	35	79	11.1	19.2	1.73	48	196	16.6	7	5	3	65	20	Vagotonic
48	75	62.7	8.5	16.2	1.91	40	222	13.4	8	4	3	90	8	Vagotonic
61	75	69	10.5	18.8	1.79	43	230	17.8	5	6	8	75	10	Vagotonic
69	65	67	10	13.9	1.39	60	171	14.7	6	5	4	35	10	Vagotonic
66	50	82	10.2	19.6	1.92	80	163	17.2	9	9	7	75	16	Vagotonic
78	25	73	10.43	19.2	1.84	15	208	13.3	8	6	3	18	13	Sympathetic-otonic
34	40	42	9	19.1	2.13	28	167	10.7	8	0	0	85	1	Sympathetic-otonic
49	31	44	8.6	22.4	2.60	40	155	14.9	10	9	0	85	19	Vagotonic
Av.	45	67	9.6	18.2	1.9	45	188	15.4	6.6	4.2	3	64	12	9 V./3 S.
28	90	75	....	....	....	50	167	15.1	7	3	0	80	9	Vagotonic
47	50	73	11.2	20.3	1.85	28	167	13.9	7	7	7	105	12	Vagotonic
74	50	58	10.1	17.9	1.72	46	196	15.7	9	3	0	48	5	Vagotonic
77	62	43	10.8	21.6	1.98	5	278	20.6	11	8	6	83	25	Vagotonic
45	41	65	11.8	20.6	1.74	40	208	14.7	9	11	13	62	20	Vagotonic
26	55	70	11.4	17.3	1.52	35	185	15.8	4	0	0	52	20	Vagotonic
68	31	32	10.6	14.3	1.35	20	238	19.5	8	8	6	110	15	Sympathetic-otonic
83	47	74	13	21.6	1.65	26	167	....	21	12	8	45	8	Sympathetic-otonic
36	92	76	9.9	26.2	2.67	43	...	....	2	4	0	95	12	Sympathetic-otonic
70	130	37.7	13.4	23.9	1.79	45	167	16.1	6	7	8	68	3	Vagotonic
12	80	72	10.7	19.2	1.79	32	208	20.8	6	0	0	55	4	Sympathetic-otonic
64	45	56	12	19.1	1.59	30	208	16.8	11	3	2	90	15	Sympathetic-otonic
Av.	65	61	11.4	20	1.8	34	199	16.9	8.5	5.5	4.1	74	15	7 V./5 S.

with 61). They have a lower level of blood calcium (9.9 as compared with 11.3) and less potassium (18.2 as compared with 20), but a slightly higher value for the K/Ca ratio. The serum globulins are increased 45 per cent as compared with 34 per cent, while both the cholesterol and the lecithin levels are lower. The reaction to tuberculin is less marked (6.6, 4.2 and 3 mm. for twenty-four, thirty-six and seventy-two hour readings, as compared with 8.4, 5.5 and 4.1 mm.). The McClure-Aldrich sodium chloride disappearance time is shorter, as is also the time of the reaction to ice.

When we turn to the reaction to the subcutaneous injection of epinephrine hydrochloride, the results in the cases of rapidly fatal disease are of considerable interest. The results are preponderatingly vagotonic, while those in the cases in which the patients lived longest were generally sympatheticotonic.

B. DETAILED STUDY OF THE REACTIONS OF PERSONS WITH TUBERCULOSIS

CONTENTS

Blister Time
Permeability of the Capillaries
Inflammatory Index
Calcium, Potassium and the K/Ca Ratio
Protein
Globulins
Basal Metabolic Rate
Vascular Reactions to Epinephrine
CO_2 Combining Power
Cholesterol
Lecithin
Cholesterol/Lecithin Ratio
Nonspecific Leukocytic Reaction to Aolan
Corpuscles/Plasma Ratio
Ice Reaction Time
Kromayer Light Reaction Time
McClure-Aldrich Salt Solution Test
Rumpel-Leede Endothelial Reaction
Intracutaneous Reactions to
    Epinephrine
    Thyroxin
Reaction to Tuberculin, at Twenty-Four, Forty-Eight and Seventy-Two Hours
Tuberculosis Complement Fixation

BLISTER TIME

In a study of the blister time of tuberculous persons in relation to our group of 100 "normal" men, we pointed out that the persons with roentgen evidence of active tuberculosis (chronic) have, in general, a longer blister time; and in a previous study,[1] we demonstrated that the blister time of those with moderately advanced tuberculosis was prolonged over that of the 100 "normal" men, but that, with advance of the disease, the blister time shortened progressively. The average blister time of our group of 100 "normal" men was 7.5 hours; for the twenty truly normal persons in this group, it was 6.8 hours. For those with roentgen evidence of active tuberculosis, it was 8.4 hours, and for the group of eighty-three tuberculous patients it was 7.4 hours.

To obtain a survey of the relation of the blister time of the tuberculous patients to the clinical status and to the status in the other tests,

1. Levinson, S. A., and Petersen, W. F.: Am. Rev. Tuberc. **15**:681, 1927.

we have prepared chart 1, as well as a table of averages for the results of the examinations of the twenty persons with the shortest, and the twenty with the longest blister time.

Explanation of Charts.—As chart 1 is typical for the other charts of this series, we shall explain it in some detail:

The original blister time curve for the clinical material used in the study reported in part III has been retained. It begins with an individual blister time of 3.5 hours and ends with a group blister time of 15 hours. The diamond indicates the range of the blister time of the truly normal persons, extending from a "low" of 6 to a "high" of 9 hours. In addition, symbols at the bottom designate the position on

TABLE 1.—*Comparison of the Groups with the Short, the Medium and the Long Time for the Appearance of the Cantharides Blister, with Regard to Clinical Status*

Clinical Classification of Patients	Short Blister Time (20 Patients)	Medium Blister Time (37 Patients)	Long Blister Time (20 Patients)
As to Type of Tuberculosis			
Minimal	10%	16%	35%
Moderately advanced	25%	27%	45%
Far advanced	65%	57%	20%
	100%	100%	100%
As to Prognosis			
Good	25%	27%	50%
Fair	40%	35%	20%
Poor	35%	38%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	35%	45%
Stationary	45%	46%	30%
Losing	10%	19%	25%
	100%	100%	100%

this original curve of the truly normal persons and these showing healed and those giving roentgenologic evidence of active tuberculosis.

On this original curve, we have superimposed the curve of the determinations made on the eighty-three tuberculous patients, and have recorded their individual numbers on the curve. Adjacent symbols indicate (*X*) the death of the patient [2] or (#) that there was pleural effusion.

In the horizontal columns at the top of the curve, we have indicated the clinical status of the patient. For instance, the first patient represented on the curve (no. 26) is recorded as having had a moderately advanced tuberculosis with a poor general prognosis, and as being stationary in weight when examined.

When we examine the curve, we find that the range of the blister time is from 4.5 to 14 hours, that patients with pleural effusion appear

2. Patients 26, 70, 64, 36 and 12 died after the charts were in the hands of the printer. The symbols for these have therefore not been recorded.

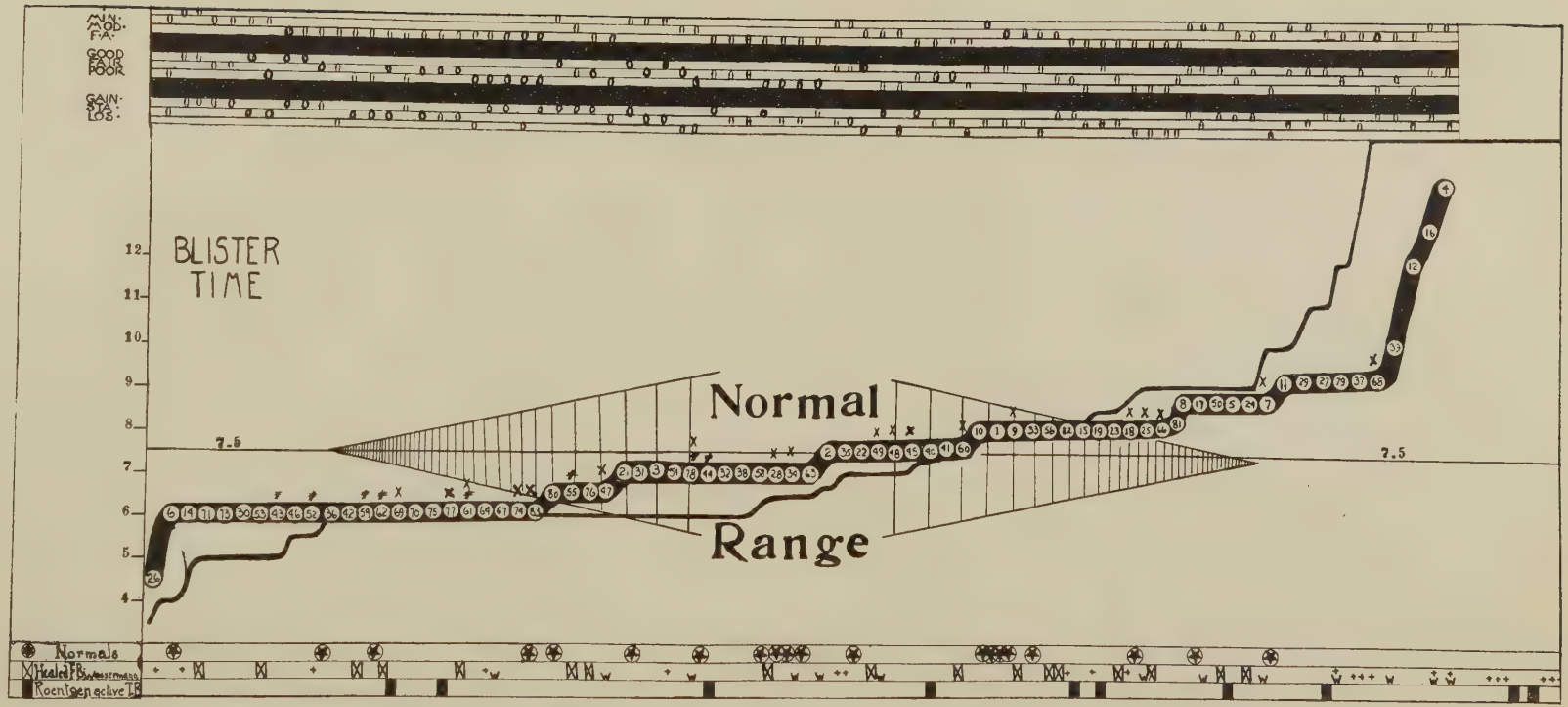

Chart 1.—The blister time curve in patients with tuberculosis. The curve has been superimposed on the original blister time curve for the miscellaneous clinical groups of part III. The original curve begins with a blister time of 3.5 hours, shown by one person, and ends with a blister time of 15 hours, which was shown by a group. The diamond indicates the range of the blister time in the truly normal persons (from 6 to 9 hours). The symbols at the bottom designate the positions on the original curve of the truly normal persons, the persons showing healed tuberculous lesions and those giving roentgen evidence of active tuberculosis.

The individual numbers of the eighty-three patients with tuberculosis are recorded on this curve, the adjacent symbols indicating (X) a patient who died, and (#) one that showed pleural effusion. In the horizontal columns at the top, the clinical status of each patient is indicated.

All succeeding charts in this part of the paper are constructed similarly.

at the lower end of the curve and that those who died are apparently uniformly scattered.

In analyzing the results of the examination under consideration in relation to the clinical conditions, we have arbitrarily selected twenty at each end of the curve and have compared them with the middle group. This analysis gives the results shown in table 1. It is evident that the

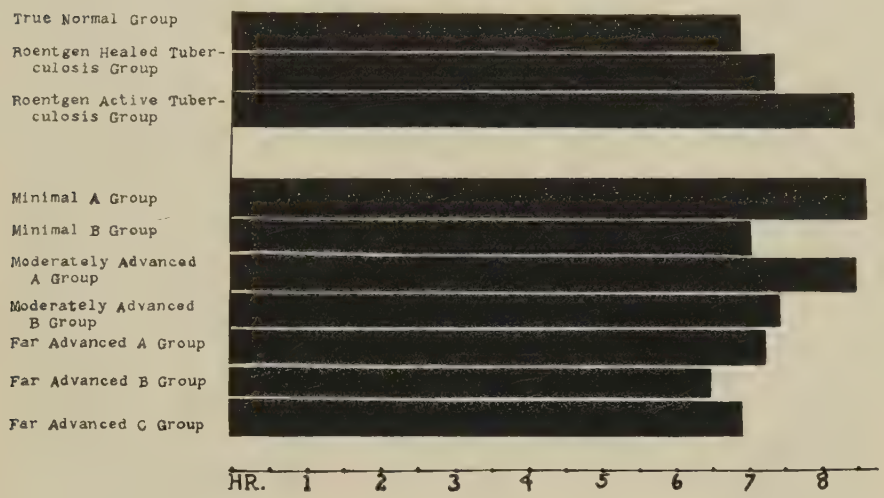
True Normal Group
Roentgen Healed Tuberculosis Group
Roentgen Active Tuberculosis Group
Minimal A Group
Minimal B Group
Moderately Advanced A Group
Moderately Advanced B Group
Far Advanced A Group
Far Advanced B Group
Far Advanced C Group
HR. 1 2 3 4 5 6 7 8

Chart 2.—The blister time curve in the 100 "normal" men of part I.

TABLE 2.—*Comparison of the Averages for the Results of the Examinations of the Groups with the Shortest and the Longest Blister Times*

Blister Time, Hours	Globulin (per Cent of Total Protein)	Protein, Mg. per 100 Cc.	Ice Reaction, Seconds	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Tuberculin at 24 Hours, Mm.	Deaths
5.92	38.66	9.32	13.9	7.22	9.55	9.4	7
9.3	31.4	8.5	10.8	5.91	7.8	7.5	6

group with the short blister time includes more persons with far advanced tuberculosis, and the group with the prolonged blister time more patients with a good prognosis. In the latter group, the percentage of those losing weight is somewhat greater.

The averages for the more significant reactions of the twenty patients with the shortest blister time are compared with those of the twenty with the longest blister time in table 2.

When we compare the different groups of the 100 "normal" men, as well as the tuberculous groups in relation to blister time, we obtain a picture (chart 2) similar to that which we previously described; i.e., the group with healed tuberculous lesions and the group with roentgenologic evidence of active tuberculosis (the latter chronic and silent) have a longer blister time than have the normal persons. Among the persons with active tuberculosis, those with the minimal and moderate manifestations have a longer time than those in whom the disease is far advanced, whose blister time progressively shortens.

PERMEABILITY OF THE CAPILLARIES

When we examine the permeability curve (chart 3), we note that the cases of the "normal" group that gave roentgenologic evidence of active tuberculosis (lowest horizontal line) are represented in the low range of the curve. On the other hand, those in the series of

TABLE 3.—*Comparison of the Groups with the Low, the Medium and the High Permeability of the Capillaries, with Regard to Clinical Status*

Clinical Classification of Patients	Low Permeability (20 Patients)	Medium Permeability (37 Patients)	High Permeability (20 Patients)
As to Type of Tuberculosis			
Minimal	30%	16%	20%
Moderately advanced	20%	43%	25%
Far advanced	50%	41%	55%
	100%	100%	100%
As to Prognosis			
Good	45%	27%	30%
Fair	30%	37%	40%
Poor	25%	36%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	40%	40%
Stationary	27%	40%	35%
Losing	33%	20%	25%
	100%	100%	100%

eighty-three tuberculous patients, who died, appear in equal numbers at both ends of the curve. However, the duration of clinical activity, as brought out in table 10 of part VIII A (p. 181) is markedly different.

The patients with pleural exudate are, with one exception (no. 52), found toward the upper end of the curve. The association of exudative reactions and increased permeability seems evident.

In examining for the relation between the clinical status and the permeability of the capillaries, percentages were determined as recorded in table 3. No striking differences are revealed in this classification; the group with less permeable capillaries has the largest percentage with good prognosis, but no significant relation of permeability to gain or loss in weight is shown.

Table 4 brings together the averages for the more significant reactions of the twenty persons with low and the twenty with high permeability.

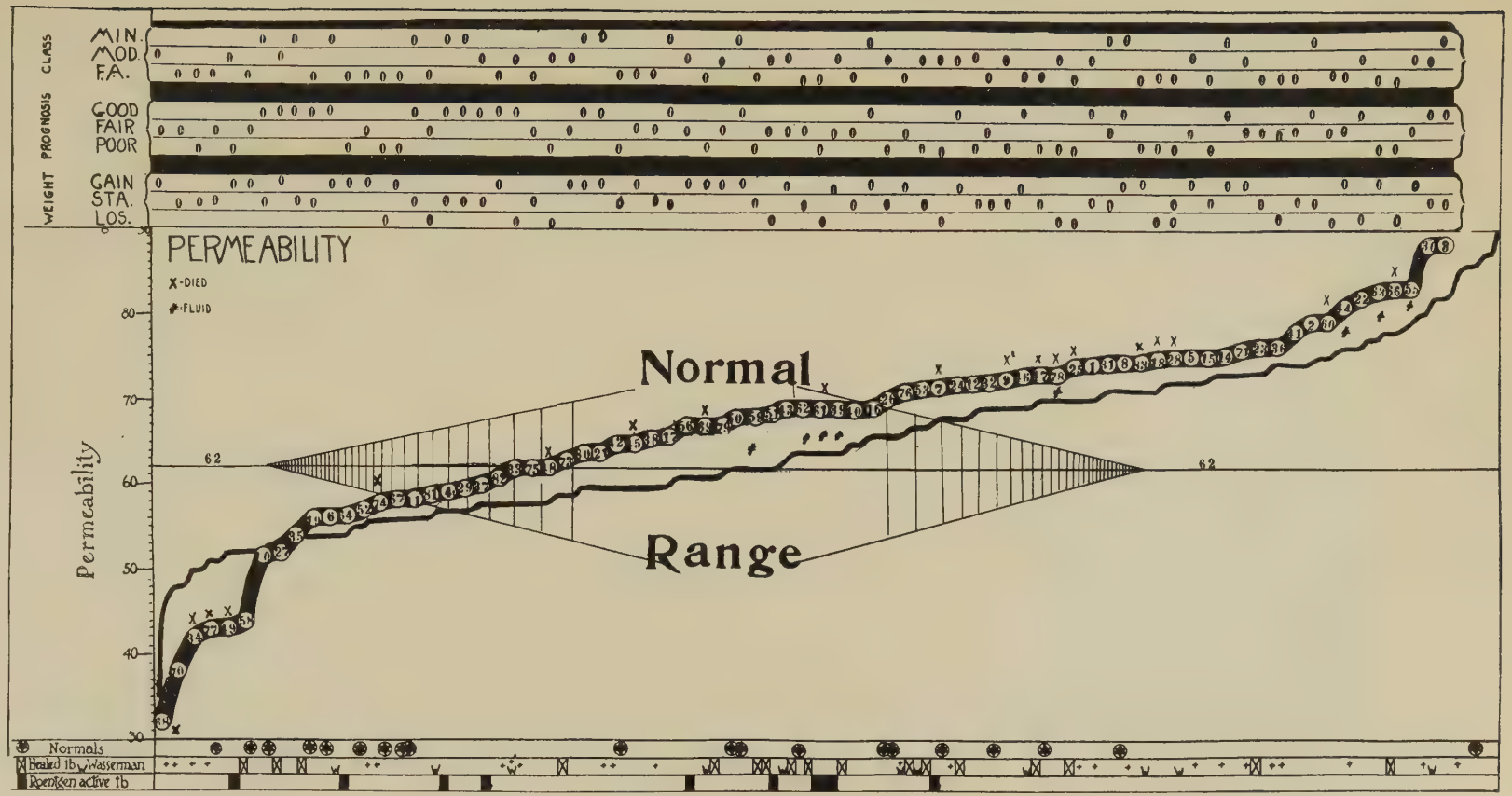

Chart 3.—The curve of capillary permeability in patients with tuberculosis. The chart is explained in the legend for chart 1.

In the group with low permeability the blister time is somewhat longer, the calcium level is higher, the value of the K/Ca ratio is lower, the total protein is greater but the globulins are less, and the time for the absorption of the salt solution is somewhat longer.

In previous papers we called attention to the relation of capillary permeability to tuberculosis—the association of increased permeability with clinical progression, etc. The results of the examinations recorded here confirm our previous work.

TABLE 4.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Permeability of the Capillaries*

Capillary Permeability	Blister Time, Hours	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Protein, Mg.	Globulin, per Cent of Total Protein	Reaction to Tuberculin at 24 Hours, Mm.	CO_2 Combining Power	NaCl Solution Absorption, Minutes	Deaths
54	7.7	10.6	19.3	1.8	9.92	25	8.7	55.5	80	7
78	7.1	10.3	20.2	2	8.4	36	8.3	57	70	6

INFLAMMATORY INDEX

In the foregoing studies of blister time and capillary permeability, it was shown that short blister time and high permeability were, in general, associated with activity. The inflammatory index, taking both factors into consideration (permeability/blister time), merely confirms this general observation.

When we examine chart 4, we observe that the inflammatory index of the entire tuberculous group is somewhat greater than that of the group of "normal" persons and miscellaneous clinical patients, and we find the majority of those who died, as well as of the patients with effusion, having an inflammatory index above the normal average of 8.2. The persons who gave roentgenologic evidence of active tuberculosis appear toward the lower end of the curve.

When we analyze the twenty cases of low inflammatory index, the thirty-seven of intermediate index and the twenty of high index in relation to clinical status, we obtain the percentages set forth in table 5. It is apparent that the cases of far advanced tuberculosis more frequently occupy the middle and the high range of the curve; that the prognosis is better at the low end and poorest in the higher region and, finally, that gain or loss in weight is not directly related.

In examining table 6, in which a comparison is made between the twenty cases at one extreme of the curve and the twenty at the other extreme, the following observations seem of interest: The groups do

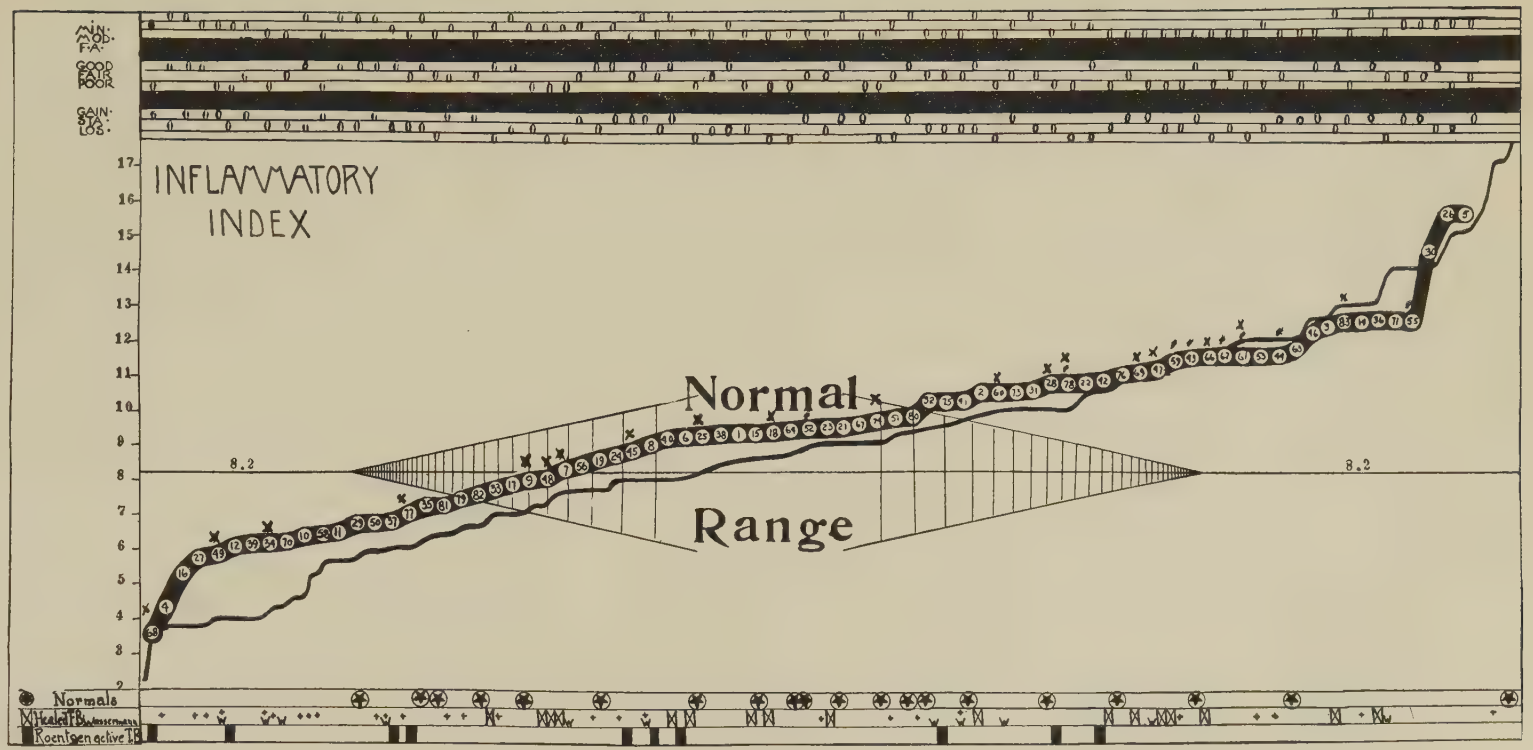

Chart 4.—The curve of the inflammatory index.

TABLE 5.—*Comparison of the Groups with the Low, the Medium and the High Values of the Inflammatory Index, with Regard to Clinical Status*

Clinical Classification of Patients	Low Index (20 Patients)	Medium Index (37 Patients)	High Index (20 Patients)
As to Type of Tuberculosis			
Minimal	35%	20%	10%
Moderately advanced	35%	30%	30%
Far advanced	30%	50%	60%
	100%	100%	100%
As to Prognosis			
Good	45%	30%	25%
Fair	30%	35%	30%
Poor	25%	35%	45%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	30%	50%
Stationary	50%	40%	35%
Losing	5%	30%	15%
	100%	100%	100%

TABLE 6.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the Inflammatory Index*

Inflammatory Index	Blister Time, Hours	Capillary Permeability	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Globulin, per Cent of Total Protein	Protein, Mg.	Age	Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Endothelial Reaction	Daranyi Reaction	Deaths
6.3	8.85	55.69	10.6	19.6	1.85	21.8	9.113	31.6	14.02	5.69	5+ 15—	10+ 8—	6
12.33	6.25	79.9	10.8	19.22	1.78	32.7	8.72	27.6	15.02	6.84	8+ 12—	13+ 5—	6

not differ in blood chemistry, but the group with the high index has more globulin, less protein, greater intracutaneous reactivity to epinephrine and a greater number each of positive endothelial reactions and positive Daránvi reactions.

CALCIUM *

The literature on the subject of the calcium and the potassium of the blood in tuberculosis is extensive. We shall refer to it but briefly.

Voorhoeve [3] is of the opinion that the actual calcium balance in a tuberculous patient is of no significance, since decalcification is relative, depending on the amount of calcium supplied. In a small series of cases, he carefully studied the amount of calcium that was needed in the diet to maintain calcium balance and found no striking differences between

* Read before the Section on Pathology and Physiology at the Seventy-Ninth Annual Session of the American Medical Association, Minneapolis, June 13, 1928.

3. Voorhoeve, N.: Deutsches Arch. f. klin. Med. **110**:231, 1913.

tuberculous and nontuberculous subjects. The analysis of Halverson [4] is interesting in that his determination of the calcium content of the blood of patients with advancing tuberculosis and of those convalescing from tuberculosis revealed that in persons with incipient tuberculosis (of whom those on a milk diet showed marked improvement) the value of the calcium in the serum was normal and fairly constant. In no case was the calcium value increased above the normal by a calcium diet. In patients with advanced tuberculosis the variations were greater, and patients who were improving showed, on the average, slightly higher values than did those who were not improving. No marked deviations from the normal, however, were observed in the calcium content of the serum of patients in the various stages of pulmonary tuberculosis.

A review of the literature on the therapeutic use of calcium in tuberculosis reveals a considerable body of clinical observation indicating an inhibitory effect on the tuberculosis itself, as well as on certain of its complications; a certain amount of evidence that favorable results are not obtainable, and a complete lack of convincing experimental evidence in support of calcium therapy. The hypothesis of a decalcification or demineralization in tuberculosis, according to Maver and Wells,[5] does not receive support from the most carefully conducted investigations. There is no demonstrable deficiency of calcium in the blood or tissues in tuberculosis, and the feeding of calcium salts does not appreciably increase the amount of calcium in the blood when this is already normal. Experiments conducted by Maver and Wells showed that guinea-pigs on an ordinary laboratory diet exhibited some variations in the calcium content of the same tissue in different animals and of different tissues in the same animals; yet, averaged in a series of animals, the results were not far from identical, being generally lowest for the liver and highest for the lymph nodes, but not far from the content of the blood—that is, from 10 to 13 mg. of calcium for each 100 Gm. moist weight. These studies have failed to produce experimental evidence to support the empirical clinical evidence that the administration of calcium has a healing influence on the course of tuberculous infection.

Determinations of the calcium concentration of the human serum as determined by Barkus [6] reveal a slightly increased value in the groups with destructive and destructive-proliferative tuberculosis. The values obtained in the group with proliferative disease were normal values and those in the group with atrophic manifestations of the disease were decreased.

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4. Halverson, J. O.; Mohler, H. K., and Bergeim, Olaf: Calcium in Blood, J. A. M. A. **68**:1309 (May 5) 1917.

5. Maver, M., and Wells, H. G.: Am. Rev. Tuberc. **6**:649, 1922.

6. Barkus, O.: Am. Rev. Tuberc. **9**:61, 1924.

Observations made by Matz [7] on the blood of both normal and tuberculous subjects show that there is little variation in the calcium content of the serum. Schoenheit [8] noted that values for calcium in the blood plasma of normal persons, determined after ashing it, were similar to the values found by others, but that those for the blood plasma of tuberculous patients were considerably less.

According to Greisheimer and Van Winkle,[9] tuberculosis is not characterized by a demineralization. Patients who regularly drink a liberal amount of milk tend to show higher calcium levels than those who refuse it. The taking of cod liver oil does not markedly increase the calcium in the plasma of tuberculous adults even when there is clinical improvement. There is no constant difference in calcium content as between the sexes; nor is there a constant difference as between ages, although the tendency is toward lower values with increasing age. Examinations were made by Brockbank [10] in seventy cases of pulmonary tuberculosis, and the value of the calcium in the serum was found varying between 8.6 and 12 mg. per hundred cubic centimeters, the normal value being 10 mg. per hundred cubic centimeters of serum. When the cases were graded according to their severity, it was observed that the average amount of calcium in the serum was decreased when the disease was acute, and was increased when the lesions had healed, with proportionate results in the intermediate stages. The difference amounted to 20 per cent. The calcium was not diminished in patients who were coughing up blood, as compared with patients in a similar stage of the disease but without that symptom. It was found that calcium, if given by mouth, failed to alter the level of the serum calcium materially, but when given intravenously it raised the serum content of calcium above the normal for forty-eight hours.

Nearly 100 estimations made by Ellman [11] show that the calcium content of the blood in pulmonary tuberculosis is within normal limits (from 9 to 11 mg. per hundred cubic centimeters); but this calcium content can be raised from the minimum to the maximum with corresponding improvement in the patient's general condition by calcium or parathyroid therapy. Krömecke,[12] as well as Rosenstein and Schmidke,[13] found an increase in the blood calcium in cases of tuberculosis with a favorable prognosis.

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7. Matz, P. B.: Am. Rev. Tuberc. **11**:250, 1925.
8. Schoenheit, E. W.: Am. J. M. Sc. **170**:689, 1925.
9. Greisheimer, E. M., and Van Winkle, C. C.: Am. Rev. Tuberc. **15**:270, 1927.
10. Brockbank, W.: Quart. J. Med. **20**:431, 1927.
11. Ellman, P.: Tubercle **9**:162, 1928.
12. Krömecke, Franz: Beitr. z. Klin. d. Tuberc. **57**:467, 1924.
13. Rosenstein and Schmidke: Beitr. z. Klin. d. Tuberc. **59**:199, 1924.

When our patients are grouped on the basis of the classifications of the National Tuberculosis Association, the relation of clinical status to calcium and potassium values is not clear (table 7). It will be seen that our group with minimal A disease has the highest value of the K/Ca ratio and all the more advanced cases far lower values, but there is no progression or regularity.

TABLE 7.—*Comparison of the Calcium Levels and of the Potassium Levels of the Blood of Tuberculous Patients Grouped on the Basis of the Classifications of the N. T. A.*

Group, Classified as to Tuberculosis	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio
Minimal A	9.1	20.8	2.27
Minimal B	10.7	18.5	1.73
Moderately advanced A	10.8	17.1	1.6
Moderately advanced B	10.2	19.6	1.92
Far advanced A	9.8	19	1.93
Far advanced B	10.5	19.8	1.87
Far advanced C	10.5	18.4	1.75

TABLE 8.—*Comparison of the Calcium Levels and of the Potassium Levels of the Blood of Tuberculous Patients Grouped According to the Weight Curve*

Group, Classified as to Weight Curve	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio
Gaining	10.6	18.9	1.8
Stationary	10.4	20.1	1.96
Losing	10.2	17.7	1.73

TABLE 9.—*Comparison of the Calcium Levels and Potassium Levels of the Blood of Tuberculous Patients Grouped on the Basis of Prognosis*

Group, Classified as to Prognosis	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio
Gaining—continued to gain	10.7	18.5	1.75
Gaining—later declined	10.6	18.6	1.77
Stationary	9.1	19.8	1.97
Losing—later gained	9.8	21	2.17
Losing—continued to decline	10.2	18.1	1.79

When the patients are classified in accordance with the weight curve, the values for the groups are as recorded in table 8. Here we have a definite reduction of the calcium as we pass from the gaining to the losing group, the losing group giving the lowest value of the K/Ca ratio.

Finally, in table 9, we present the results when the grouping is made on the basis of prognosis. It is obvious that the groups who were gaining had the highest calcium levels but the high level in the last group may seem confusing. We are of the impression that the two groups present totally different pictures of calcium metabolism despite the similarity of the determinations. In the groups of patients who are gaining we have the organism maintaining a high calcium level as part of the picture of resistance, and this without loss from the body—such patients are, as a rule, in calcium balance. In the group of patients who are losing we have

a fairly high calcium level, but it represents calcium leaving the tissue and passing out from the body—these patients usually show a negative calcium balance.

The three intermediate groups seem to bear out this assumption, the stationary group having the lowest amount. Certainly, the calcium values seem of greater importance than the potassium values or the values of the K/Ca ratios in all the clinical correlations.

These assumptions seem to be made more probable when we recall the calcium values of the blood of the so-called "normal" groups

TABLE 10.—*Comparison of the Calcium Levels and the Potassium Levels of the Blood of the "Normal" Groups*

Clinical Group	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio
Truly normal	9.7	20.3	2.1
Having healed tuberculosis (Roentgen)	10.5	20.8	1.98
Having active tuberculosis (Roentgen)*	9.6	20.1	2.08

* Silent lesions, probably chronic.

TABLE 11.—*Comparison of the Groups with the Low, the Medium and the High Calcium Levels, with Regard to Clinical Status*

Clinical Classification of Patients	Low Calcium (20 Patients)	Medium Calcium (35 Patients)	High Calcium (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	20%	25%
Moderately advanced	35%	25%	45%
Far advanced	40%	55%	30%
	100%	100%	100%
As to Prognosis			
Good	40%	37%	35%
Fair	35%	20%	40%
Poor	25%	43%	25%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	28%	55%
Stationary	35%	40%	45%
Losing	20%	32%	0
	100%	100%	100%

(table 10). Here, again, the high calcium level occurs in the healed (resistant) group; the group with only roentgen evidence of activity (chronic tuberculosis) has a low level.

We turn now to an analysis of the determinations made for the group and arranged in curves from low to high levels.

The range of calcium values for the series is from a low of 8.2 to a high of 13.4, and it is at once apparent, on inspection of chart 5, that a considerable number of the patients at the low end of the curve have died, while the patients with pleural effusion are scattered to a greater extent.

The distribution of the clinical types on the curve is shown in table 11. The most striking feature is the fact that none of the twenty patients at

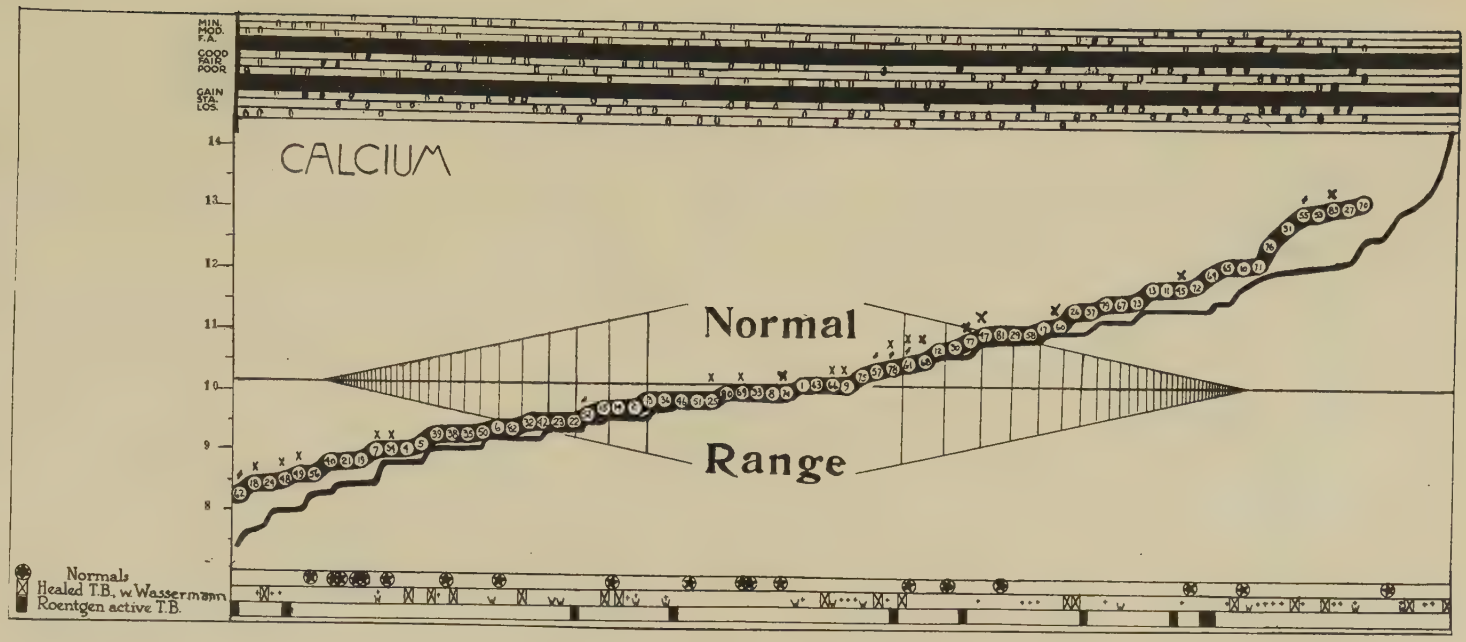

Chart 5.—The calcium curve.

the high end of the calcium curve were losing weight, the entire group either gaining or remaining stationary at the time of examination.

In table 12, the averages for the results of the examinations of the patients with the extremely high or the extremely low calcium values are shown. The following observations seem of interest: The group with the low calcium level has, of course, a higher K/Ca ratio; the inflamma-

TABLE 12.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Calcium Levels*

Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Blister Time, Hours	Inflammatory Index	Globulin, per Cent of Total Protein	Protein, Mg.	CO_2 Combining Power	Reaction to Thyroxin, Flare, Mm.	NaCl Disappearance Time (McClure-Aldrich), Min.	Corpuscles/Plasma Ratio	Reaction to Epinephrine, Vagotonic	Reaction to Epinephrine, Sympathicotonic	Deaths
8.93	19.4	2.17	8	8.46	27	8.42	55.4	3.8	89.1	41	17	5	6
12.1	19.8	1.62	6.9	9.5	34.2	9.08	57.3	2.97	65.7	39.6	12	8	5

tory index is somewhat lower because of a longer blister time, the McClure-Aldrich sodium chloride disappearance time is somewhat longer, the corpuscle/plasma ratio is a little higher and the number of "vagotonic" reactions to epinephrine is somewhat greater.

POTASSIUM

When we examine the potassium curve in chart 6, the relation to deaths would indicate that these are more likely to occur in the patients with the high potassium range. The clinical distribution of the cases on the curve is shown in table 13. No clearcut influence of the potassium levels on any clinical feature tabulated is revealed. This is evident, too,

TABLE 13.—*Comparison of the Groups with the Low, the Medium and the High Potassium Levels, with Regard to Clinical Status*

Clinical Classification of Patients	Low Potassium (20 Patients)	Medium Potassium (35 Patients)	High Potassium (20 Patients)
As to Type of Tuberculosis			
Minimal	20%	23%	30%
Moderately advanced	45%	28%	25%
Far advanced	35%	49%	45%
	100%	100%	100%
As to Prognosis			
Good	40%	28%	50%
Fair	30%	28%	30%
Poor	30%	44%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	51%	25%
Stationary	35%	31%	60%
Losing	25%	18%	15%
	100%	100%	100%

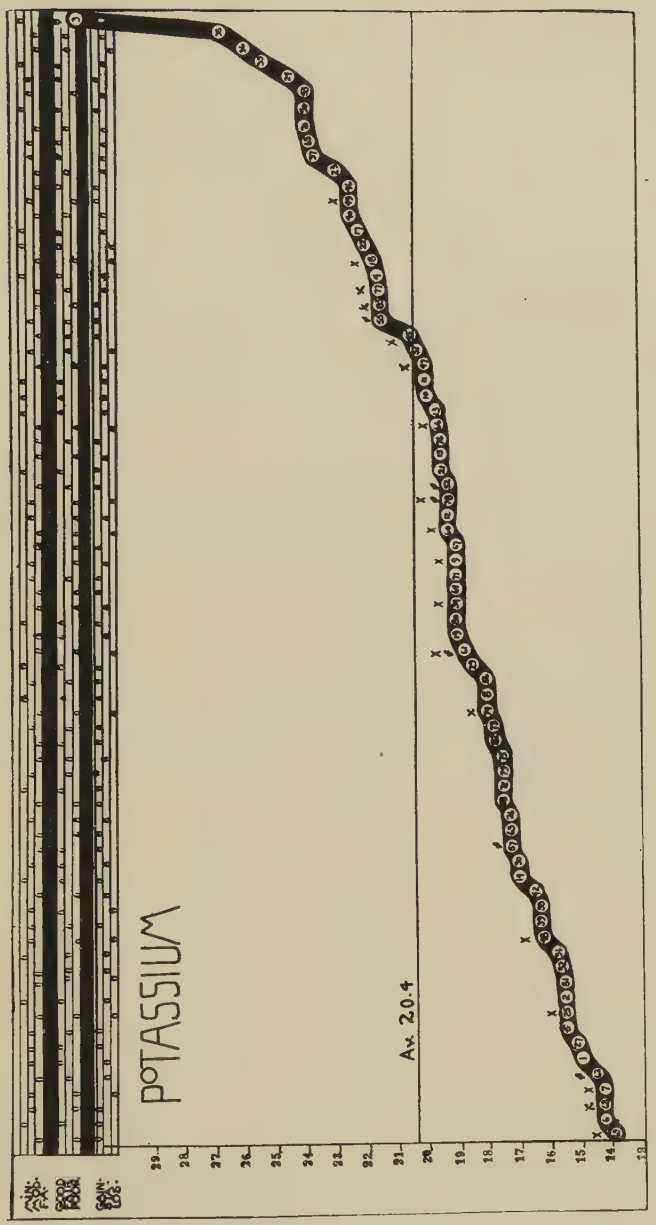

Chart 6.—The potassium curve.

when we inspect the averages of the other determinations for the two extreme groups (table 14). The only fact of apparent interest is the greater size of the reactions to thyroxin in the group with the low level of potassium. In part 1, table 1, the relation between the reactions of the skin to thyroxin and the potassium level is made evident.

TABLE 14.—*Comparison of the Results of the Examinations of the Groups with the Low and the High Potassium Levels*

Potassium, Mg. per 100 Cc.	Calcium, Mg.	K/Ca Ratio	Age	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Corpuscles/Plasma Ratio	Deaths
15.5	10	1.56	28.8	9.6	3.35	40.7	5
23.7	10.2	2.37	33.8	8.4	2.55	38.1	6

THE K/CA RATIO

The K/Ca ratio has apparently much less influence on the tuberculous process than the actual amount of calcium. In the curve in chart 7, the deaths are well distributed along the various levels, as are the cases with pleural effusion.

TABLE 15.—*Comparison of the Groups with the Low, the Medium and the High Values of the K/Ca Ratio, with Regard to Clinical Status*

Clinical Classification of Patients	Low Ratio (20 Patients)	Medium Ratio (35 Patients)	High Ratio (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	20%	20%
Moderately advanced	45%	28%	25%
Far advanced	30%	52%	45%
	100%	100%	100%
As to Prognosis			
Good	35%	31%	50%
Fair	30%	25%	35%
Poor	35%	44%	15%
	100%	100%	100%
As to Weight Curve			
Gaining	55%	34%	35%
Stationary	30%	43%	45%
Losing	15%	23%	25%
	100%	100%	100%

The clinical status of the groups with the low, medium and high values of the K/Ca ratio is made evident in the percentages recorded in table 15. The only apparently significant feature is that with a high value of the ratio the prognosis is apparently better.

The averages for various determinations in the examination of the extreme groups show no striking differences (table 16). The group

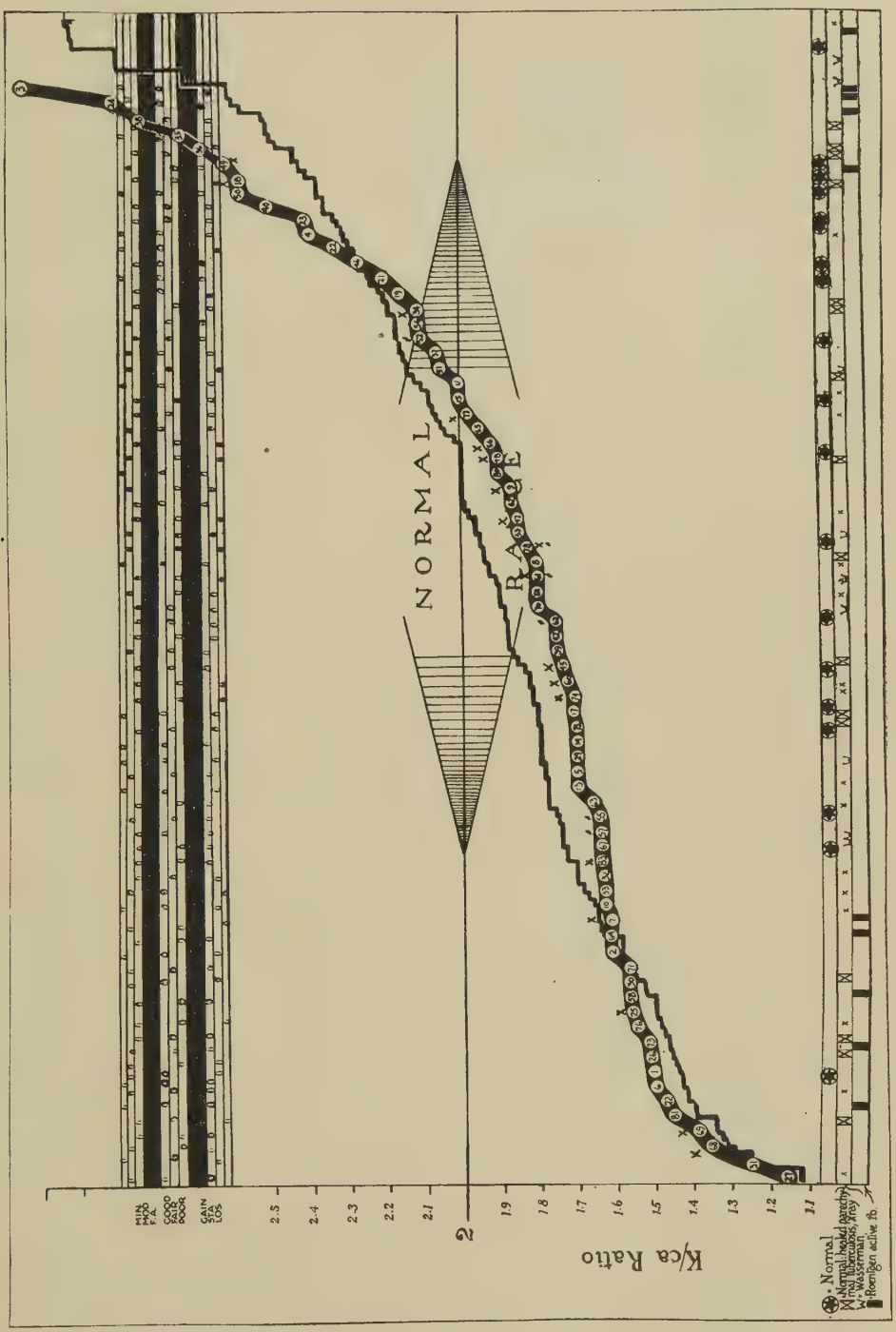

Chart 7.—The curve of the K/Ca ratio.

with the low value of the ratio weighs slightly less, has a slightly lower value of the cholesterol lecithin ratio, a smaller flare at the site of injection of epinephrine and a larger wheal at the site of injection of thyroxin, and the salt solution resorption time is a little shorter.

TABLE 16.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the K/Ca Ratio*

K/Ca Ratio	Calcium, Mg. per 100 Cc.	Potassium, Mg.	Inflammatory Index	Pulse Pressure	Weight/Length Ratio	Lecithin, Mg.	Cholesterol/Lecithin Ratio	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	NaCl Resorption (McClure-Aldrich) Time, Minutes	Corpuscles/Plasma Ratio	Deaths
1.49	11.1	16.5	9.3	45.6	1.91	173.5	1.16	6.16	9.65	2.4	71.6	38.1	6
2.44	9.29	22.6	8.79	51.4	2.06	156	1.26	7.56	8.3	3.85	84.7	40	4

PROTEIN

The average percentage of the protein in the blood serum of the "normal" group was determined as 8. For the serum of our tuberculous group, this was 8.8, and, as one surveys chart 8, it appears that patients with more advanced tuberculosis have a higher concentration. Thus, there appear to be more deaths in this region of the curve and also more cases with pleural effusion.

TABLE 17.—*Comparison of the Groups with the Low, the Medium and the High Levels of Protein in the Serum, with Regard to Clinical Status*

Clinical Classification of Patients	Low Protein (20 Patients)	Medium Protein (41 Patients)	High Protein (20 Patients)
As to Type of Tuberculosis			
Minimal	35%	22%	10%
Moderately advanced	40%	26%	25%
Far advanced	25%	52%	65%
	100%	100%	100%
As to Prognosis			
Good	60%	36%	15%
Fair	30%	26%	40%
Poor	10%	38%	45%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	34%	55%
Stationary	40%	53%	15%
Losing	15%	13%	30%
	100%	100%	100%

The percentage distribution of the patients with the low and the high concentrations of protein on the basis of clinical status is given in table 17. It appears that more cases of far advanced tuberculosis occur at the upper end, at which, also, the prognosis is poorest. Curiously,

Chart 8.—The protein curve.

both gain and loss in weight are most marked here, reflecting, probably, the fact that in many instances these gains represent fluctuations in the water balance.

Table 18, presenting the results of the examinations of the two extreme groups, offers a number of contrasts, some of which are contradictory. The group with the low protein has less globulin, fewer positive tuberculin and Darányi reactions, a higher value of the corpuscles/plasma ratio, a greater number of sympatheticotonic vascular reactions, a longer blister time, but a somewhat higher permeability, and a higher value of the K/Ca ratio.

TABLE 18.—*Comparison of the Results of the Examinations of the Groups Having the Lowest and the Highest Concentrations of Protein in the Serum*

Protein, Mg. per 100 Cc.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Albumin	Globulin, per Cent of Total Protein	Reaction to Tuberculin, Mm.	Darányi Reaction	Corpuscles/Plasma Ratio	Reaction to Epinephrine	Deaths
7.454	7.6	70.5	9.5	9.79	19.4	2	77.2	22.8	9+ 8—	11+ 7—	40.7	9V 11S	2
10.526	6.8	61.9	9.07	10.71	19	1.77	60.2	39.8	14+ 6—	16+ 3—	37.7	13V 7S	7

GLOBULINS

There can be little doubt concerning the relation of the increase in globulins to the prognosis in tuberculosis. With this increase in the globulins in cases of far advanced tuberculosis, are to be associated the changes in the sedimentation time, the increase in fibrinogen, the various flocculations, which depend on the colloidal instability, etc.

When we examine the curve in chart 9, it is immediately apparent that the high end has the majority of deaths. The cases showing pleural exudations are equally distributed.

The percentage analysis of the cases plotted on the curve with regard to clinical condition is shown in table 19. The majority of the cases of far advanced tuberculosis occur at the high end and the prognosis here is poorest. On the other hand, the relation of gain or loss of weight to the curve is uncertain. While, of course, in the low end of the curve a majority of the patients are gaining or are stationary, in the high end the gaining, the stationary and the losing are about equally divided. As mentioned in the corresponding discussion of the total protein, this is probably to be explained on the basis of the fluctuation of the water balance, which occurs so readily in these cases of far advanced tuberculosis.

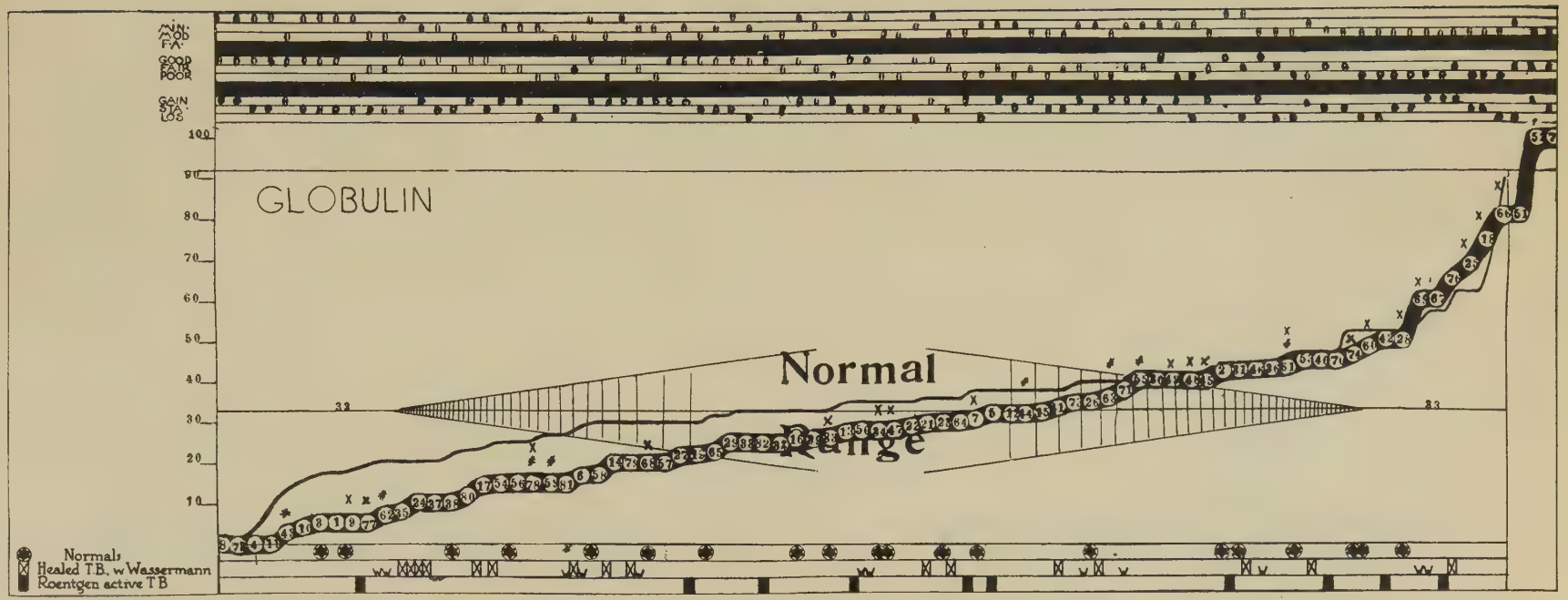

Chart 9.—The globulin curve.

Table 20, in which the two extreme groups are compared, shows the following conditions, many of which correspond with the observations in the groups having the high and the low values of total protein: The group with the low globulins has a longer blister time, a lower inflammatory index, a higher value of the K/Ca ratio, less protein, a higher value of the corpuscles/plasma ratio, fewer positive tuberculin and Daranyi reactions and a greater number of vagotonic reactions to epinephrine.

TABLE 19.—*Comparison of the Groups with the Low, the Medium and the High Levels of Globulins, with Regard to Clinical Status*

Clinical Classification of Patients	Low Globulins (20 Patients)	Medium Globulins (42 Patients)	High Globulins (20 Patients)
As to Type of Tuberculosis			
Minimal	55%	19%	5%
Moderately advanced	25%	40%	10%
Far advanced	20%	41%	85%
	100%	100%	100%
As to Prognosis			
Good	65%	38%	5%
Fair	25%	28%	40%
Poor	10%	34%	55%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	50%	30%
Stationary	60%	38%	35%
Losing	5%	12%	35%
	100%	100%	100%

TABLE 20.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Concentrations of Globulins in the Serum*

Globulins, Mg. per 100 Cc.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Albumin	Protein, Mg.	Tuberculous Complement Fixation	Daranyi Reaction	Corpuscles/Plasma Ratio	Diagnosis	Reaction to Epinephrine	Deaths
7.2	7.9	65.8	8.6	10.1	20.7	2.07	92.8	8.18	13+ Neg. 6+	12+ Neg. 8+	4.16	9 minimal 7 mod. ad. 4 far ad.	13V 7S	3
59.3	6.62	68.1	10.3	10.5	19.6	1.88	40.7	9.37	3— Neg. 17+	1— Neg. 18+	39.1	1 minimal 2 mod. ad. 17 far ad.	6V 14S	10

BASAL METABOLIC RATE

The basal metabolic rate for the tuberculous group averages +6.5, and the curve (chart 10) proportionately follows that established for our "normal" and miscellaneous clinical group. The fatal cases and the majority of those with pleural effusion are grouped at the upper end of the curve. The clinical status of each of the groups with the low, the medium and the high rates is shown in the percentages listed in table 21. In the group with the low basal metabolic rate, the cases of minimal

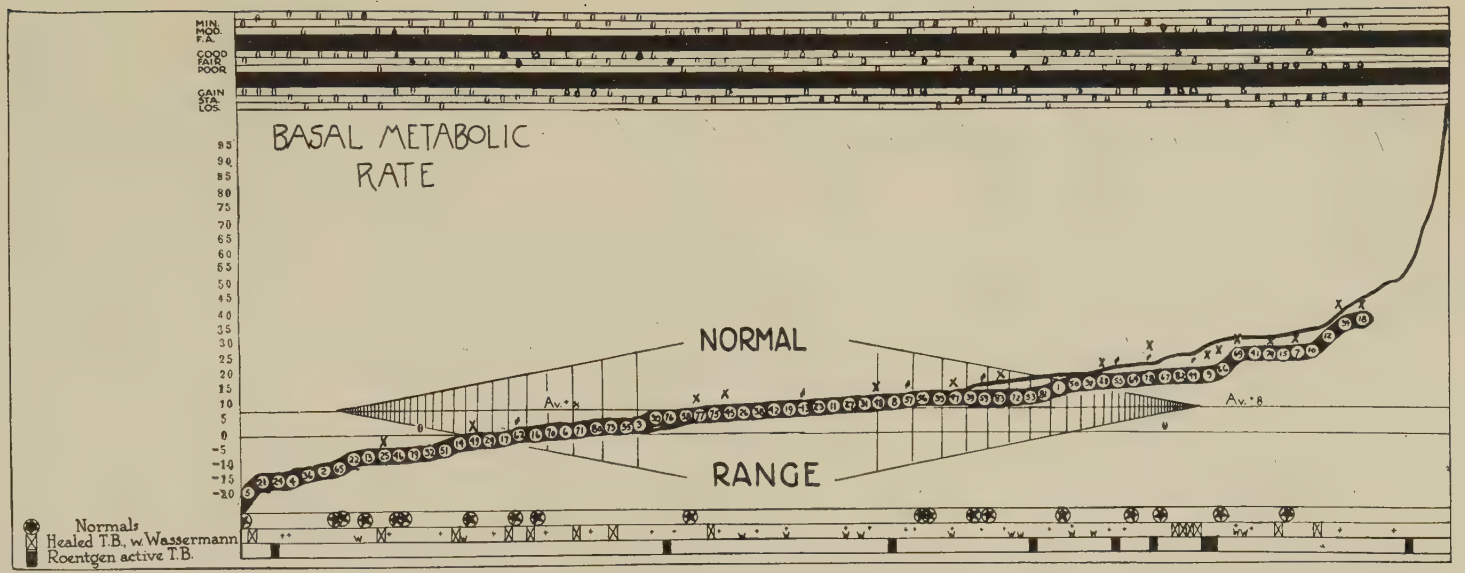

Chart 10.—The curve of the basal metabolic rate.

manifestation predominate; in the group with the high basal metabolic rate, the cases of far advanced tuberculosis. The same ratios are true for the good and the poor prognoses. There is no apparent relation to the weight curve.

In table 22, in which the groups at the ends of the curve are compared in detail, the group with the high rate is shown to have a some-

TABLE 21.—*Comparison of the Groups Having, Respectively, Low, Medium and High Basal Metabolic Rates, with Regard to Clinical Status*

Clinical Classification of Patients	Low Basal Metabolic Rate (20 Patients)	Medium Basal Metabolic Rate (35 Patients)	High Basal Metabolic Rate (20 Patients)
As to Type of Tuberculosis			
Minimal	45%	23%	10%
Moderately advanced	30%	31%	30%
Far advanced	25%	46%	60%
	100%	100%	100%
As to Prognosis			
Good	60%	40%	20%
Fair	30%	37%	15%
Poor	10%	23%	65%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	43%	35%
Stationary	40%	48%	40%
Losing	20%	9%	25%
	100%	100%	100%

TABLE 22.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Basal Metabolic Rates*

Basal Metabolic Rate	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Min.	CO_2 Combining Power	Ice Reaction Time, Seconds	Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Diagnosis	Prognosis	NaCl Solution Resorption Time, Minutes	Deaths
— 8.6	9.8	19.6	2	95.9	55.7	13.3	14.36	6.21	8 minimal 7 mod. advanced 5 far advanced	12 good 6 fair 2 poor	80.8	3
+21.3	10.3	19.3	1.87	71	57.2	9.3	16.37	6.93	2 minimal 6 mod. advanced 12 far advanced	4 good 3 fair 13 poor	69	11

what lower value of the K/Ca ratio, a shorter Kromayer light erythema time and a shorter ice reaction time and a larger flare on the injection of epinephrine.

VASCULAR REACTIONS TO EPINEPHRINE

In papers VIII D and VIII E,[14] we describe the reactions of our tuberculous group to the subcutaneous injections of epinephrine.

14. Article VIII D, A Study of the Reaction to Epinephrine in Tuberculous Patients, p. 260; Article VIII E, Composite Curves of Cardiovascular Reactions Following Injections of Epinephrine in Tuberculous Patients, p. 269.

Both the individual curves and their analysis on the basis of clinical status, as well as composite curves, are presented in detail.

CO_2 COMBINING POWER

We might expect that the CO_2 combining power of the patient would show relatively little concurrence with the clinical activity. In chart 11,

TABLE 23.—*Comparison of the Groups with the Low, the Medium and the High CO_2 Combining Power, with Regard to Clinical Status*

Clinical Classification of Patients	Low CO_2 Combining Power (20 Patients)	Medium CO_2 Combining Power (39 Patients)	High CO_2 Combining Power (20 Patients)
As to Type of Tuberculosis			
Minimal	30%	25%	5%
Moderately advanced	10%	36%	45%
Far advanced	60%	39%	50%
	100%	100%	100%
As to Prognosis			
Good	40%	41%	20%
Fair	30%	25%	40%
Poor	30%	34%	40%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	44%	45%
Stationary	45%	39%	30%
Losing	20%	18%	25%
	100%	100%	100%

TABLE 24.—*Comparison of the Results of the Examinations of the Groups Having the Lowest and the Highest CO_2 Combining Power*

CO_2 Combining Power	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Min.	Ice Reaction Time, Seconds	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Flare, Mm.	Corpuscles/Plasma Ratio	Daranyi Reaction	Deaths
49.16	10.3	18.9	1.84	103	13.6	6.24	1.32	40.75	11+ 7—	5
63.18	10.26	17.9	1.74	83.1	9.4	7.17	3.4	38.2	18+	5

our strictly normal material is scattered over the entire range of the normal curve, while the cases in which there is roentgen evidence of active tuberculosis tend toward the upper end. The curve for our tuberculous material indicates that deaths, as well as pleural effusion are scattered.

The general clinical status of the patients represented on the curve also indicates that there is no significant difference clinically between the extremes (table 23).

Table 24, in which the groups with the extremely high and the extremely low CO_2 combining power are compared, shows the following

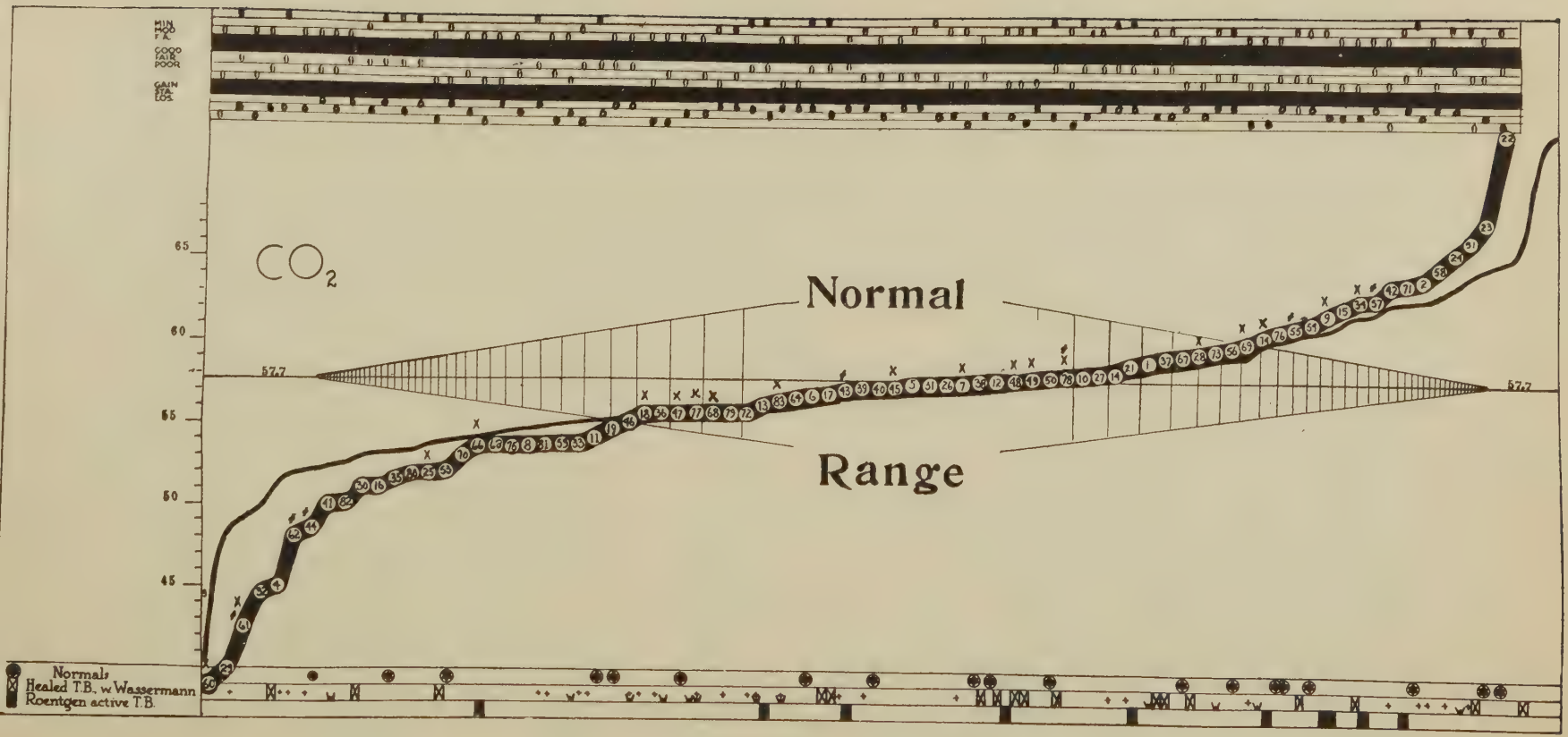

Chart 11.—The curve of the CO_2 combining power.

differences between the groups: The group with the low CO_2 combining power has a higher level of potassium and a higher value of the K/Ca ratio, a longer Kromayer light erythema time, a longer ice reaction time, a smaller flare at the site of the intracutaneous injection of epinephrine and thyroxin and fewer positive Darányi reactions.

CHOLESTEROL

The association of high cholesterol values with more favorable types of tuberculous infection has been repeatedly suggested. In chart 12, our values for the series of tuberculous patients are considerably lower than those for the "normal" persons and persons with miscellaneous clinical conditions. If it is permissible to draw conclusions from the limited material, it appears, too, that the cases of healed tuberculosis among our "normal" and miscellaneous groups are more apt to be associated with high cholesterol values.

TABLE 25.—*Comparison of the Groups with the Low, the Medium and the High Cholesterol Content in the Blood, with Regard to Clinical Status*

Clinical Classification of Patients	Low Cholesterol (20 Patients)	Medium Cholesterol (38 Patients)	High Cholesterol (20 Patients)
As to Type of Tuberculosis			
Minimal	15%	23%	20%
Moderately advanced	15%	37%	40%
Far advanced	70%	40%	40%
	100%	100%	100%
As to Prognosis			
Good	30%	37%	35%
Fair	20%	30%	45%
Poor	50%	33%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	30%	44%	45%
Stationary	50%	37%	45%
Losing	20%	19%	10%
	100%	100%	100%

TABLE 26.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of Cholesterol in the Serum*

Cholesterol, Mg. per 100 Cc.	Diagnosis	Blood Pressure	Globulin, per Cent	Protein, Mg.	Reaction to Epinephrine, Wheal, Mm.	Reaction to Tuberculin, Mm.	Darányi Reaction	Deaths
157.7	3 minimal 3 moderately advanced 14 far advanced	109.1	39.2	8.365	15.37	8.6	15+ 1—	10
235.1	4 minimal 8 moderately advanced 8 far advanced	123.7	30.9	8.953	14.41	11.1	12+ 5—	3

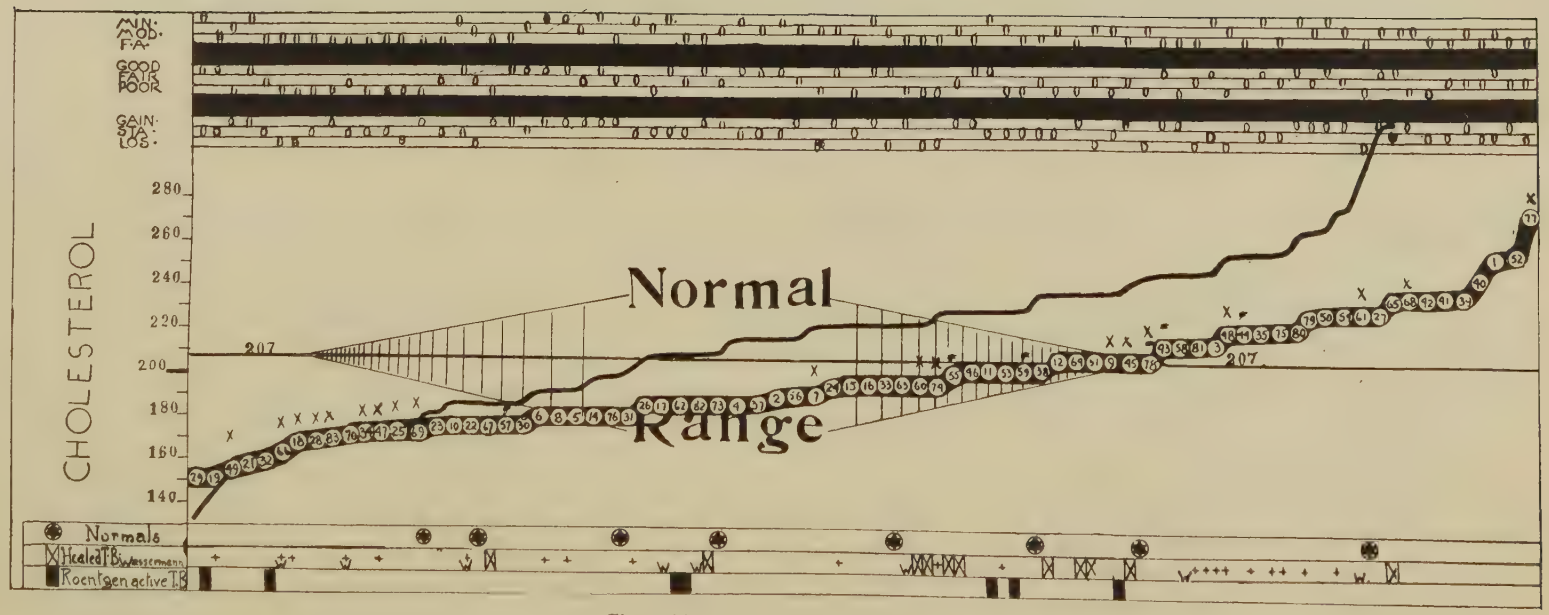

Chart 12.—The cholesterol curve.

It is rather striking that so many fatal cases are at the lower end of the curve; the cases with effusion appear more frequently at the opposite end.

The clinical status of the groups with the low, the medium and the high cholesterol values is shown in the percentages set forth in table 25. The group with the lowest cholesterol values contains more cases of far advanced tuberculosis with poor prognosis; many of the patients in this group, however, are either stationary or gaining in weight. The group with the highest cholesterol values contains a greater number of cases of moderately or far advanced tuberculosis; the majority of the patients in this group have a fair or good prognosis and are either stationary or gaining in weight.

Table 25, in which the twenty patients at the low end of the curve are compared with the twenty at the high end, indicates that the low group has a lower blood pressure, more globulin and a smaller reaction to tuberculin. The low group also is characterized by ten fatal cases, as compared with three in the high group.

LECITHIN

An analysis of the lecithin curve in chart 13 from the point of view of the clinical status of the patients represented in it reveals a clinical distribution as tabulated in table 27. The group at the low end of the curve shows the cases of far advanced tuberculosis to be in the majority, with poor or, at best, fair prognosis. The high group, on the other hand, shows more cases of minimal tuberculosis and more with a good prognosis. The relation of these groups to the weight curve is uncertain.

TABLE 27.—*Comparison of the Groups with the Low, the Medium and the High Lecithin Values, with Regard to Clinical Status*

Clinical Classification of Patients	Low Lecithin (20 Patients)	Medium Lecithin (36 Patients)	High Lecithin (20 Patients)
As to Type of Tuberculosis			
Minimal	10%	20%	40%
Moderately advanced	35%	27%	30%
Far advanced	55%	53%	30%
	100%	100%	100%
As to Prognosis			
Good	15%	38%	55%
Fair	40%	30%	15%
Poor	45%	32%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	50%	25%
Stationary	40%	33%	60%
Losing	20%	17%	15%
	100%	100%	100%

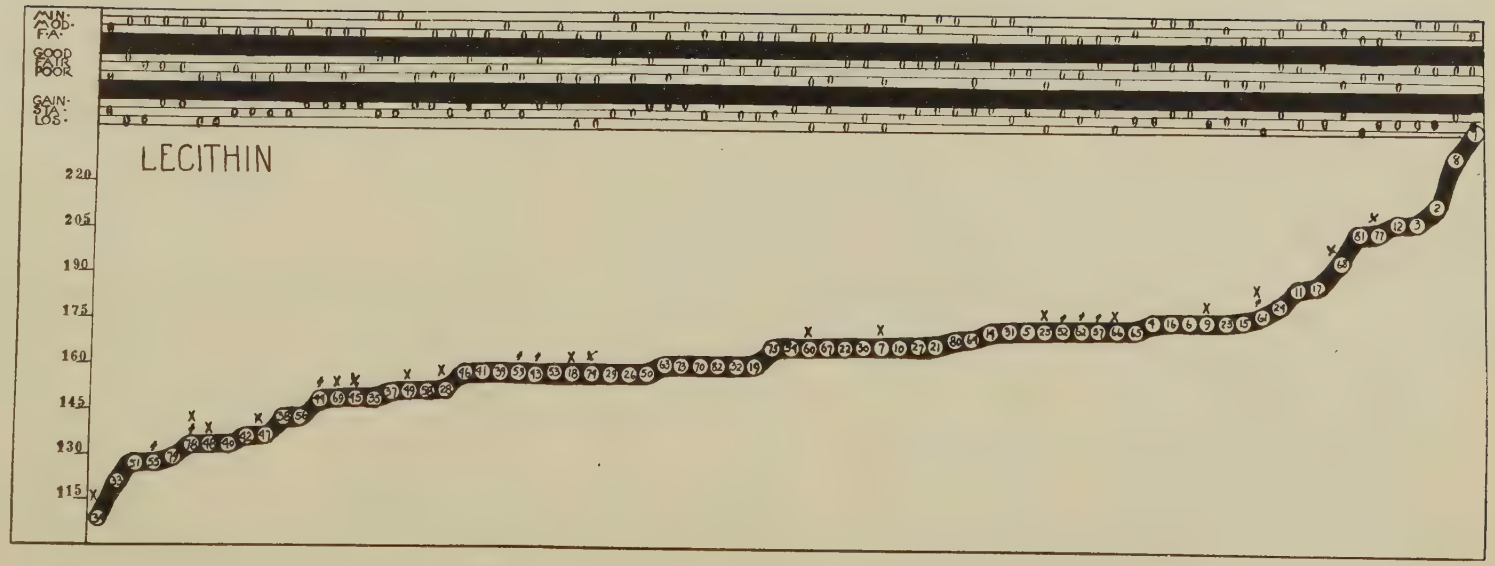

Chart 13.—The lecithin curve.

The table in which the groups at the extreme ends of the curve are compared (table 28) shows the following: The low group has a shorter blister time, higher globulin, a longer Kromayer light erythema time, a larger flare at the site of the injection of epinephrine, as well as a larger reaction to thyroxin and a greater number of positive tuberculin and Darányi reactions.

TABLE 28.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Lecithin Values of the Serum*

Lecithin, Mg. per 100 Cc.	Cholesterol/Lecithin Ratio	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Globulin, per Cent of Total Protein	Protein, Mg.	Kromayer Light Erythema Time, Min.	Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Weight/Length Ratio	Reaction to Tuberculin, Flare, Mm.	Darányi Reaction	Deaths
138	1.46	7.21	64.4	8.96	10	19.3	1.94	32.6	9.049	84	15.07	7.91	9.45	5.87	1.9	14+ 5—	14+ 4—	8
191	1.084	8.5	67.1	8.2	10.2	19.3	1.95	24	8.75	67.8	15	5.46	8.3	1.8	1.92	7+ 12—	11+ 8—	6

CHOLESTEROL/LECITHIN RATIO

Since high cholesterol and low lecithin values presumably have some prognostic significance, we have studied this ratio as it involves our material. It is apparent from a survey of the curve in chart 14 that deaths are scattered over the entire range. Here again, cases with effusion are seemingly more common with the high values.

The relation of the ratio to the clinical status of the patient as indicated in table 29 is not clear. There are more cases of moderately advanced and far advanced tuberculosis at the high end of the curve; the majority of the patients with the high values are gaining and have a

TABLE 29.—*Comparison of the Groups with the Lowest and the Highest Values of the Cholesterol/Lecithin Ratio, with Regard to Clinical Status*

Clinical Classification of Patients	Low Value (20 Patients)	Medium Value (36 Patients)	High Value (20 Patients)
As to Type of Tuberculosis			
Minimal	45%	14%	10%
Moderately advanced	15%	40%	40%
Far advanced	40%	46%	50%
	100%	100%	100%
As to Prognosis			
Good	60%	33%	20%
Fair	15%	22%	55%
Poor	25%	45%	25%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	35%	50%
Stationary	55%	44%	30%
Losing	10%	21%	20%
	100%	100%	100%

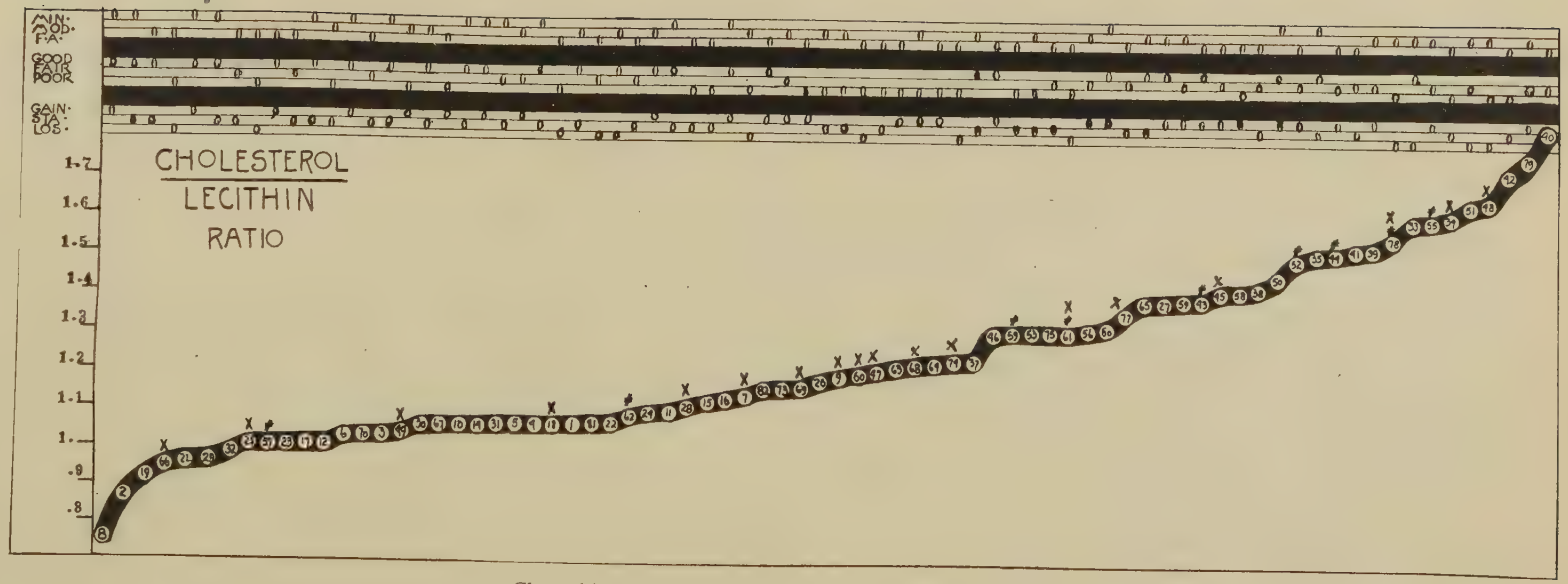

Chart 14.—The curve of the cholesterol/lecithin ratio.

fair prognosis. On the other hand, in the low group there are more cases of minimal manifestation of the disease. The group has more patients with good prognosis (60 per cent) and a far greater number (90 per cent) who are either gaining or stationary. It is evident that the index is of prognostic value only when we take into consideration the stage of the tuberculous process.

As there are no apparent correlations with the results of the other tests, the tables have been omitted. It may be recalled that determinations of cholesterol in our group of 100 "normal" men showed few correlations with other determinations (table 1, part 1).

NONSPECIFIC LEUKOCYTIC REACTION TO AOLAN

When a bland protein is intracutaneously injected, a peripheral vascular constriction takes place, with a coincident leukopenia. At the same time, a splanchnic dilatation apparently occurs and the leukocytes accumulate for the time being in the internal organs. The degree of the shift in the leukocyte count is of value in estimating the autonomic status. Müller [15] studied the reaction in detail.

We studied such reactions in the series of patients with tuberculosis. The results of the composite curves are given in article VIII F.[16]

CORPUSCLE/PLASMA RATIO

The corpuscle/plasma ratio has been described as of definite prognostic value in tuberculosis. Chart 15 reveals that both deaths and cases of pleural effusion are uniformly distributed.

The distribution of the clinical activity with regard to the low, medium and high values of this ratio is shown in table 30. The group

TABLE 30.—*Comparison of the Groups with the Low, the Medium and the High Values of the Corpuscles/Plasma Ratio, with Regard to Clinical Status*

Clinical Classification of Patients	Low Value (20 Patients)	Medium Value (40 Patients)	High Value (20 Patients)
As to Type of Tuberculosis			
Minimal	20%	22.5%	25%
Moderately advanced	10%	40 %	35%
Far advanced	70%	37.5%	40%
	100%	100%	100%
As to Prognosis			
Good	40%	40%	30%
Fair	20%	25%	45%
Poor	40%	35%	25%
	100%	100%	100%
As to Weight Curve			
Gaining	45%	40%	40%
Stationary	35%	45%	45%
Losing	20%	15%	15%
	100%	100%	100%

15. Müller, E. F.: München. med. Wchnschr. **70**:1113, 1923.

16. Article VIII F, The Leukocytic Reaction of the Tuberculous Patient Following the Intracutaneous Injection of Aolan, p. 272.

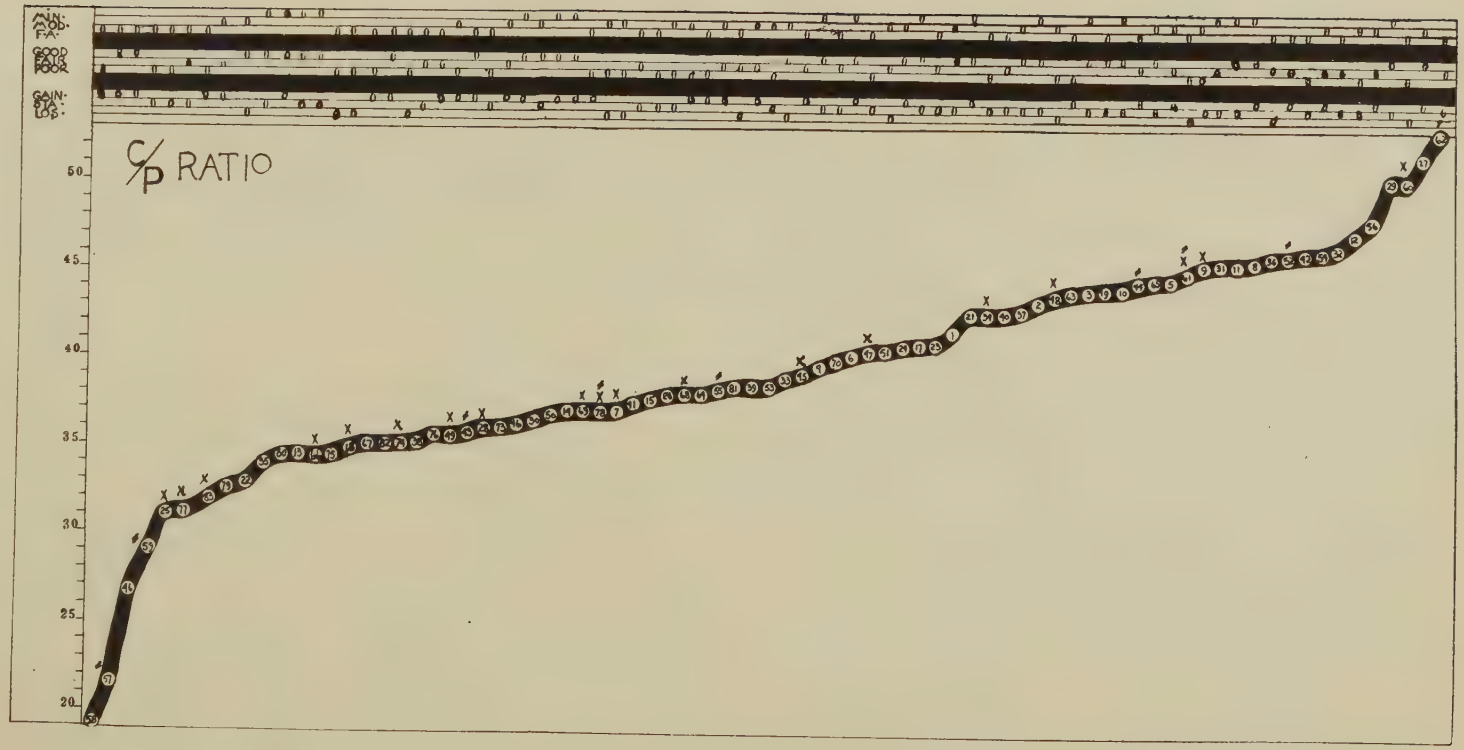

Chart 15.—The curve of the corpuscles/plasma ratio.

at the low end of the curve shows proportionately more cases of far advanced tuberculosis with poor prognosis. There is no relation to the weight curve.

TABLE 31.—*Comparison of the Results of the Examinations of the Groups with the Lowest and the Highest Values of the Corpuscles/Plasma Ratio*

Corpuscles/Plasma Ratio	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Protein, Mg.	CO_2 Combining Power	Weight/Length Ratio	Deaths
31.76	6.94	65.4	9	10.47	19.95	1.9	9.25	56.92	1.79	6
47.42	7.66	68.1	9.48	10.55	18.51	1.75	8.77	53.14	2.05	5

When we examine table 31, in which the group at the extreme ends of the curve are compared, we observe that the K/Ca ratio is higher in the low group, as are the serum protein and the CO_2 combining power, and that, as a group, these patients with the low value of the ratio in question weigh considerably less.

ICE REACTION TIME

For our group of 100 "normal" men, the ice reaction time averaged 19 seconds, while for our group of twenty actually normal persons it was reduced to 14.5 seconds. This group with the low reaction time had an average age of 40 years. The group with tuberculosis, with an average age of 31 years, should show an ice reaction time below 14.5 seconds, and we actually found it to be 12 seconds.

The curve (chart 16) indicates that both deaths and cases with pleural effusion are more common in the patients with a short ice reaction time. On the other hand, the cases in which there was roentgenologic evidence of active tuberculosis, in our "normal" series, appear more frequently with longer ice reaction time (age?).

The clinical status of the groups represented on the ice reaction curve is shown in table 32. It seems that in the low and middle regions of the curve there are more cases of far advanced tuberculosis, while the prognosis and the weight curve appear to be somewhat better in the region of the delayed ice reaction.

Table 33, in which the groups at the extreme ends of the curve are compared in detail, also indicates that the persons with a delayed reaction have a more favorable outlook. The group with the short reaction time

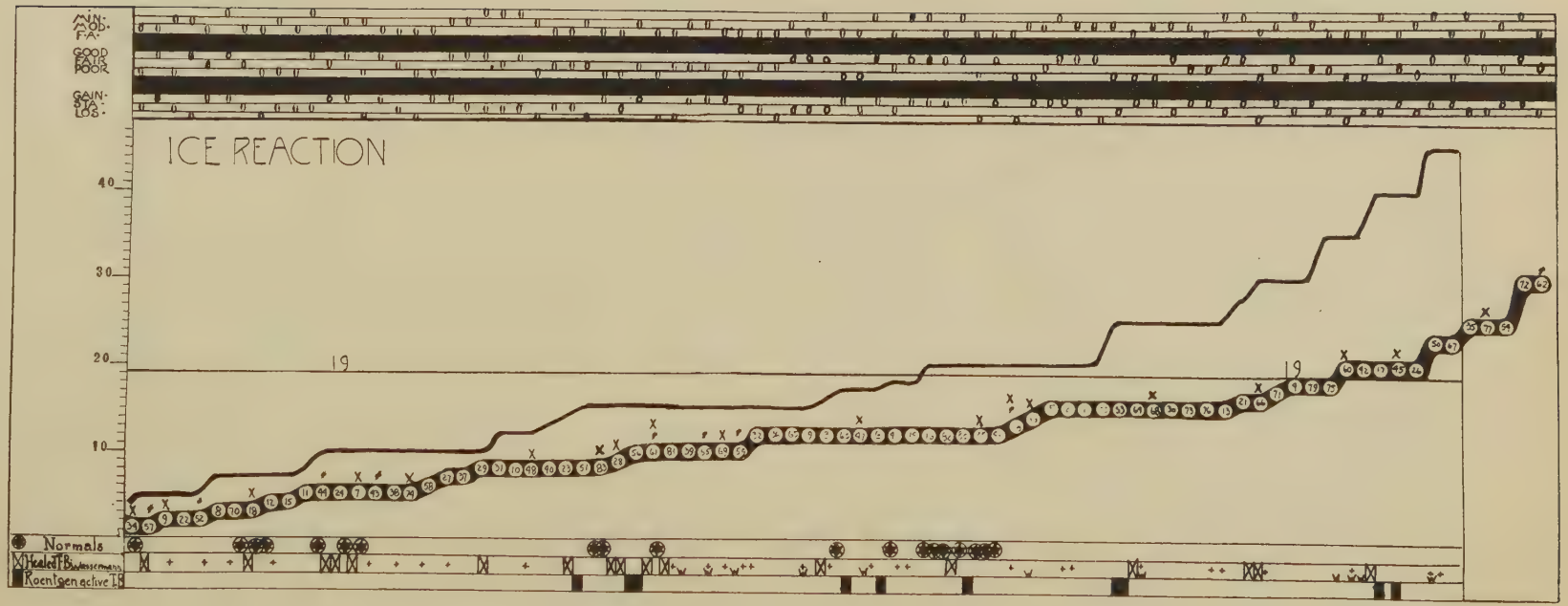

Chart 16.—The curve of the ice reaction time.

has many more cases with complications. The Kromayer light erythema time is shorter, the CO_2 combining power is higher, the wheal at the site of the injection of epinephrine is somewhat larger and the reaction to tuberculin less intense.

TABLE 32.—*Comparison of the Groups with the Short, the Medium and the Long Ice Reaction Time, with Regard to Clinical Status*

Clinical Classification of Patients	Short Time (20 Patients)	Medium Time (42 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal	10%	21%	35%
Moderately advanced	35%	30%	20%
Far advanced	55%	49%	45%
	100%	100%	100%
As to Prognosis			
Good	40%	35%	35%
Fair	20%	31%	40%
Poor	40%	34%	25%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	43%	45%
Stationary	40%	38%	45%
Losing	20%	19%	10%
	100%	100%	100%

TABLE 33.—*Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Time for the Reaction to Ice*

Ice Reaction Time, Seconds	Blister Time, Hours	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Min.	CO_2 Combining Power	Age	Reaction to Epinephrine, Wheal, Mm.	Endothelial Reaction	Reaction to Tuberculin, Mm.	Deaths
4	7.7	10.2	19.9	1.95	70	59.2	35.12	15.77	6+ 14—	7.1	8
20.7	7.2	10.6	19.5	1.84	98.6	55.42	31.8	14.42	9+ 11—	9.3	5

KROMAYER LIGHT REACTION TIME

The reactive erythema following upon the application of the Kromayer light appears somewhat more rapidly in tuberculous persons, as is evident in chart 17. While the time averages 120 minutes for our "normal" group, it is only 90 minutes for the patients with tuberculosis.

The clinical distribution is shown in table 34. The table shows clearly that it is impossible to correlate the reaction with any particular clinical phase.

Table 35, in which the groups at the extreme ends of the curve are compared in detail, also illustrates the relative similarity of the two groups and it is for this reason that we have included the averages. The

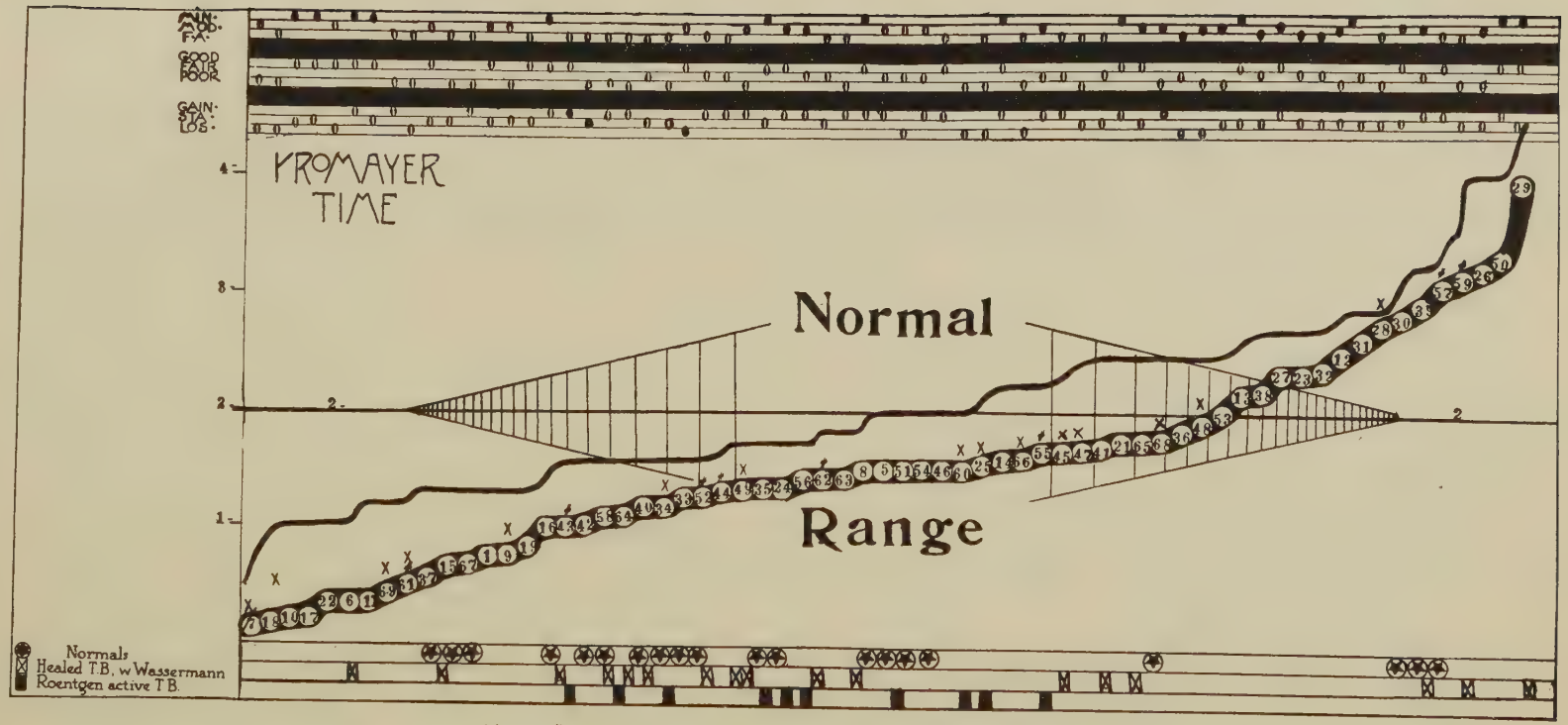

Chart 17.—The curve of the Kromayer light erythema time.

only striking difference lies in the endothelial reaction—the group with the short reaction time gives 50 per cent positive reactions as compared with 10 per cent for the group with the delayed reaction. This is confirmed when we examine the Kromayer reaction time of all the patients with the positive Rumpel-Leede endothelial reaction. It is then found to be 65 minutes as contrasted with 105 minutes for the cases in which the Rumpel-Leede endothelial reaction is negative.

TABLE 34.—*Comparison of the Groups with the Short, the Medium and the Long Time for the Appearance of Kromayer Light Erythema, with Regard to Clinical Status*

Clinical Classification of Patients	Short Time (20 Patients)	Medium Time (25 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	16%	20%
Moderately advanced	25%	32%	45%
Far advanced	50%	52%	35%
	100%	100%	100%
As to Prognosis			
Good	50%	28%	35%
Fair	0	44%	30%
Poor	50%	28%	35%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	56%	25%
Stationary	45%	28%	65%
Losing	30%	16%	10%
	100%	100%	100%

TABLE 35.—*Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Time for the Appearance of the Kromayer Light Erythema*

Kromayer Light Erythema Time, Min.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Reaction to Morphine, Wheal, Mm.	Reaction to Morphine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Endothelial Reaction	Deaths
35.8	7.62	65.8	8.8	16.57	7.2	7.4	5.1	7.35	3.72	10+ 10—	6
153.1	7.6	67.8	9.3	15.26	6.25	6.92	4.15	8.82	3.12	2+ 18—	6

MC CLURE-ALDRICH TEST

The disappearance time of intracutaneously injected salt solution, as suggested by McClure-Aldrich, seems of considerable interest in tuberculosis. Chart 18 shows that in our tuberculous patients this time varied from 15 to 190 minutes. Deaths occur more frequently in the low part of the curve; pleural effusion is more common at the high end.

The clinical status of the cases as classified on the curve is recorded in table 36. In general, the distribution of minimal, moderately advanced and far advanced tuberculosis is practically equal; the prognosis is somewhat better in the cases with delayed absorption and the weight curve is decidedly more favorable at the upper end of the curve.

TABLE 36.—*Comparison of the Groups with the Short, the Medium and the Long Resorption Time for Salt Solution, with Regard to Clinical Status*

Clinical Classification of Patients	McClure-Aldrich Salt Solution Disappearance Test		
	Short Time (20 Patients)	Medium Time (39 Patients)	Long Time (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	25%	15%
Moderately advanced	25%	28%	35%
Far advanced	50%	47%	50%
	100%	100%	100%
As to Prognosis			
Good	30%	36%	40%
Fair	20%	30%	40%
Poor	50%	34%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	30%	38%	65%
Stationary	35%	48%	20%
Losing	35%	14%	15%
	100%	100%	100%

TABLE 37.—*Comparison of the Results of the Examinations of the Groups with the Shortest and the Longest Disappearance Time for Salt Solution (McClure-Aldrich Test)*

NaCl Disappearance Time (McClure-Aldrich Test)	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mg.	K/Ca Ratio	Kromayer Light Erythema Time, Min.	Ice Reaction, Seconds	Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Reaction to Tuberculin, Mm.	Deaths
42.4	70.4	9.99	10.48	19.5	1.86	79.7	8.75	15.7	5.98	8.3	2.67	5.5	8
117.3	65.46	8.86	9.8	19.25	1.95	102.7	11.8	13.66	7.53	9.6	2.95	10.4	3

When we compare the groups at the extreme ends of the curve (table 37), the following points seem of interest: There are no apparent differences in the amount of globulin; in the group with the short time, the protein is 8.5 per cent as compared with 9 per cent for the group with the delayed disappearance. The group with the short time has greater permeability of the capillaries, a higher inflammatory index, more calcium, and much shorter Kromayer and ice reaction times. The wheal at the site of the injection of epinephrine is larger, but the flare is smaller, as is also the thyroxin wheal and the reaction to tuberculin.

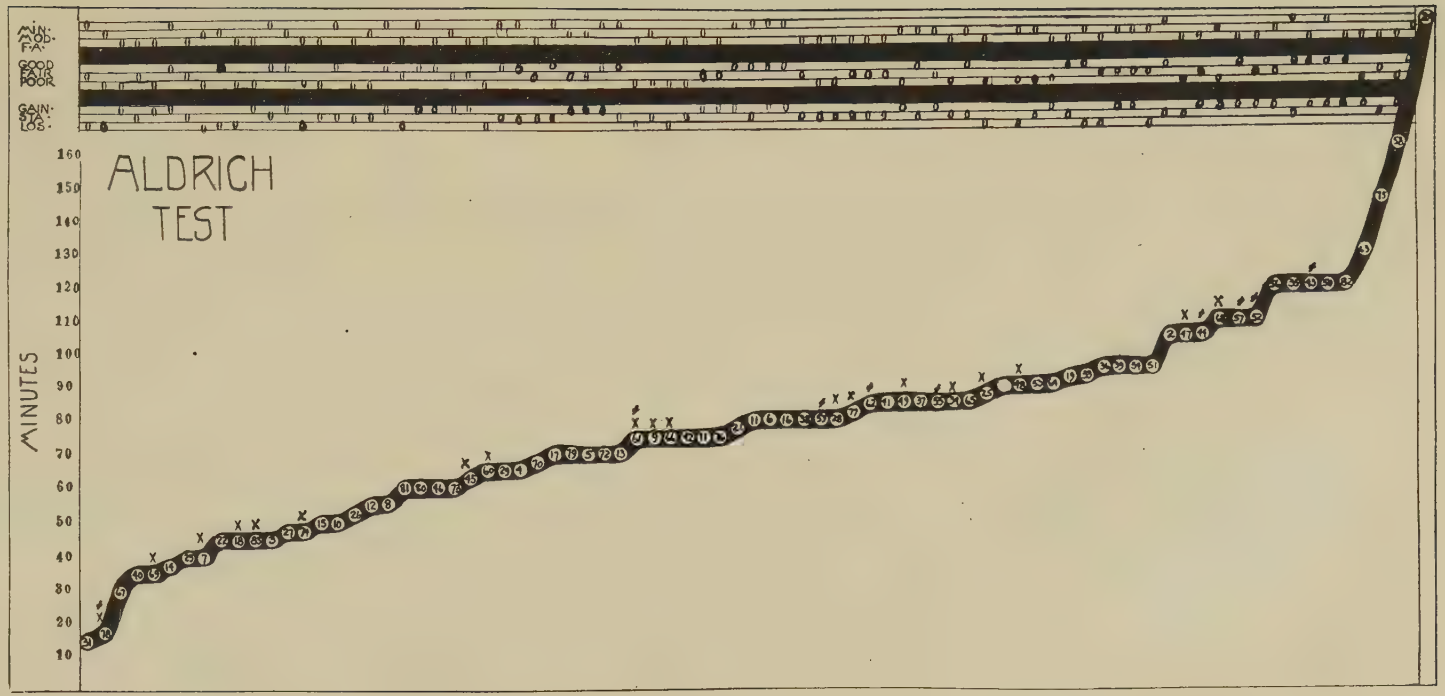

Chart 18.—The curve of the disappearance time of the salt solution in the McClure-Aldrich test.

Feldman [17] studied some thirty patients ill with terminal tuberculosis and found that the shortest absorption times were in the patients with the most toxic condition.

RUMPEL-LEEDE ENDOTHELIAL REACTION

Thirty-two of the eighty-three patients gave a positive endothelial reaction. These patients were proportionately distributed among the groups with minimal, moderately advanced and far advanced tuberculosis. There may be some significance in the fact that only one of the patients with the positive reaction had a pleural effusion; that one third of them gave a primary sympatheticotonic reaction and that their average Kromayer light erythema time was shortened to 65 minutes. (The average for the group with tuberculosis was 90 minutes.)

INTRACUTANEOUS REACTION TO EPINEPHRINE: WHEAL

The average size of the wheal at the site of the injection of epinephrine in our "normal" series was 19.2 mm. In the tuberculous group, it averaged 15.2. From the curve in chart 19, it may be noted

TABLE 38.—*Comparison of the Groups with the Smallest, the Medium and the Largest Diameters of the Wheal at the Site of the Injection of Epinephrine, with Regard to Clinical Status*

Clinical Classification of Patients	Small Wheal (20 Patients)	Medium Wheal (42 Patients)	Large Wheal (20 Patients)
As to Type of Tuberculosis			
Minimal	0	33%	20%
Moderately advanced	55%	23%	25%
Far advanced	45%	44%	55%
	100%	100%	100%
As to Prognosis			
Good	10%	46%	40%
Fair	50%	21%	30%
Poor	40%	33%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	46%	35%
Stationary	40%	31%	60%
Losing	25%	23%	5%
	100%	100%	100%

that more deaths occurred in the patients with small wheals, while cases with pleural effusion were scattered over the entire range. The clinical status of the groups with the small, the medium and the large wheals is shown in table 38. There are no cases of minimal manifestation in the group with the small wheals, and the group has either a fair or a poor prognosis. In the group with the large wheals, the prognosis seems better and more of the cases are at least stationary. The group with the most favorable prognosis seems to be that in which the wheal is intermediate.

17. Feldman, A.: Intradermal Salt Solution Test in Tuberculosis, Arch. Int. Med. **41**:549 (April) 1928.

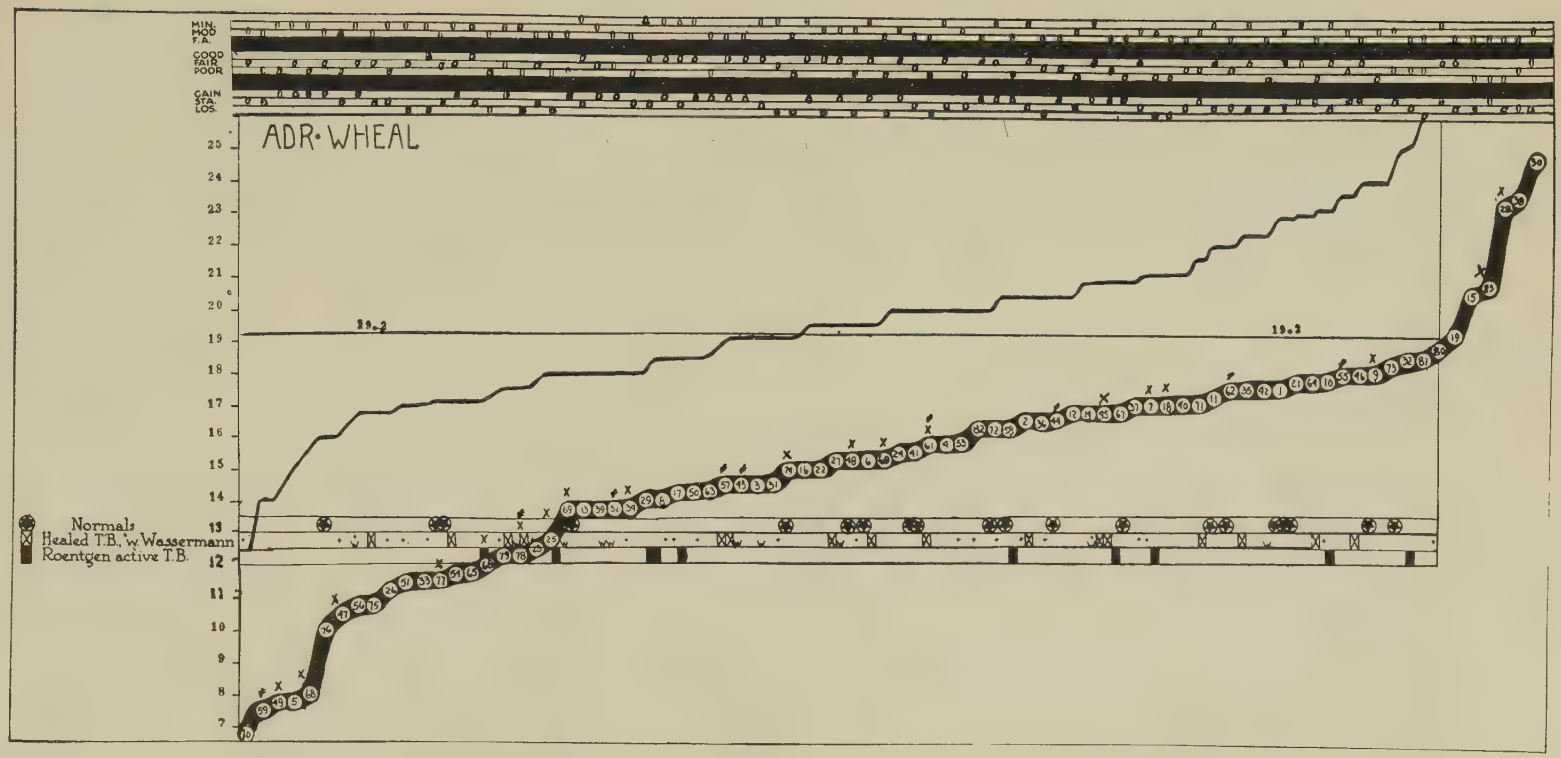

Chart 19.—The curve of the intracutaneous reaction to epinephrine (wheal).

The analysis of the results in the tests of the groups at the ends of the curve (table 39) indicates that the flare of the reaction to epinephrine and capillary permeability are somewhat greater in the group with large wheals; and the same observation holds true for the reaction to tuberculin. The absorption time for sodium chloride solution in this group is somewhat less.

TABLE 39.—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Wheal at the Site of the Injection of Epinephrine*

Reaction to Epinephrine, Wheal, Mm.	Reaction to Epinephrine, Flare, Mm.	Capillary Permeability	Kromayer Light Erythema Time, Min.	Age	NaCl Resorption Time, Minutes	Reaction to Tuberculin, Mm.	Deaths
10.47	6.32	63.6	110	29.6	82.5	9.2	8
19.22	7.844	67.6	85.8	34.5	69.1	11.9	4

INTRACUTANEOUS REACTION TO EPINEPHRINE: FLARE

In our group of "normal" men, the average flare of the reaction to epinephrine had a radius of 8.8 mm. In the patients with tuberculosis, it had a radius of 6.8 mm. As with the wheal, the curve (chart 20)

TABLE 40.—*Comparison of the Groups with the Small, the Medium and the Large Radii of the Flare at the Site of the Injection of Epinephrine, with Regard to Clinical Status*

Clinical Classification of Patients	Small Flare (20 Patients)	Medium Flare (42 Patients)	Large Flare (20 Patients)
As to Type of Tuberculosis			
Minimal	25%	23%	15%
Moderately advanced	30%	31%	40%
Far advanced	45%	46%	45%
	100%	100%	100%
As to Prognosis			
Good	35%	35%	40%
Fair	30%	26%	40%
Poor	35%	39%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	40%	38%	55%
Stationary	50%	42%	30%
Losing	10%	20%	15%
	100%	100%	100%

shows the deaths occurring in larger number in the group with the smaller flares. The clinical status of the groups with the small and the large flares is shown in table 40. There appears to be no significant relation of the size of the flare to the clinical classification, the prognosis or the weight curve; many more deaths are found in the group with the small flares.

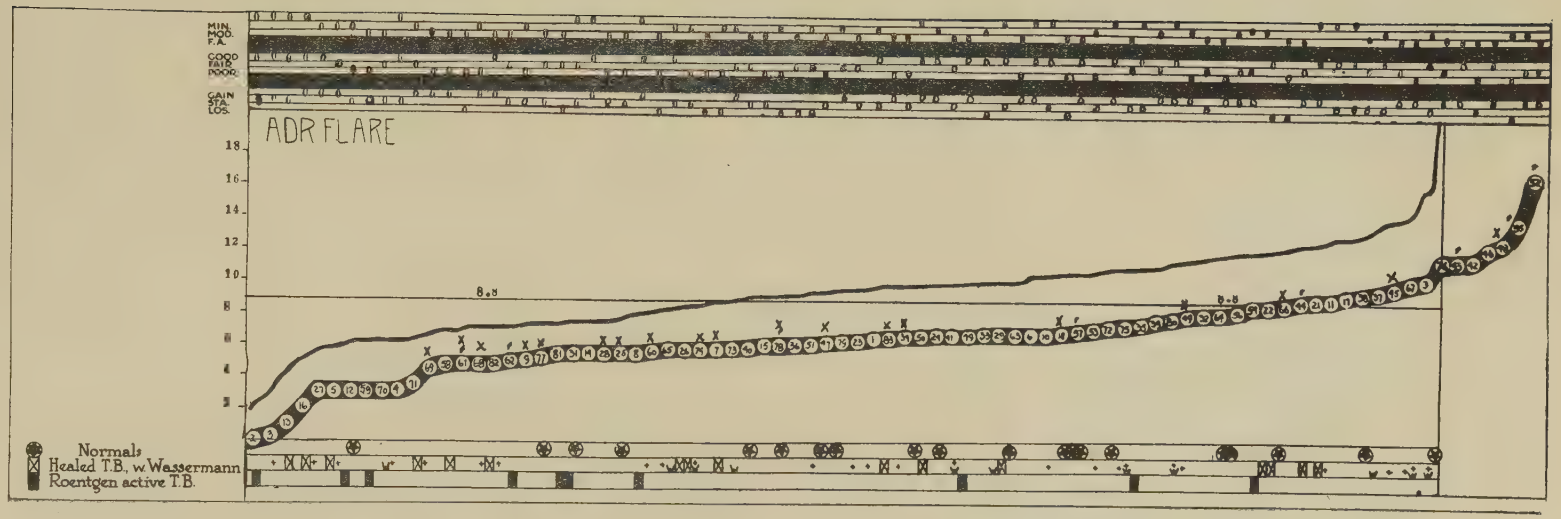

Chart 20.—The curve of the intracutaneous reaction to epinephrine (flare).

When we examine table 41, in which the group at the ends of the curve are compared in detail, we note that with the smaller flare the wheal at the site of the injection of epinephrine is somewhat smaller, and also the flare at the site of the injection of thyroxin. The blister time is somewhat longer and the capillary permeability relatively diminished so that the inflammatory index is smaller. The absorption of the sodium chloride solution is also somewhat quicker. The value of the K/Ca ratio is lower.

TABLE 41.—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Radii of the Flare at the Site of the Injection of Epinephrine*

Reaction to Epinephrine, Flare, Mm.	Reaction to Epinephrine, Wheal, Mm.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium, Mg.	Potassium, Mm.	K/Ca Ratio	Kromayer Light Erythema Time, Mm.	CO_2 Combining Power	NaCl Resorption Time, Minutes	Deaths
3.691	13.82	9.35	3.25	8	62.5	8.6	10.7	18.55	1.75	95.8	54.9	73.6	9
10.56	15.8	8.75	6.3	7.1	69.3	10	10.4	20.2	1.96	77.8	58.1	81.2	2

INTRACUTANEOUS REACTION TO THYROXIN: WHEAL

There seems to be no characteristic relation of the mortality nor any relation of the cases with pleural effusion to the size of the wheal at the site of the injection of thyroxin. When we examine the clinical status of the patients as grouped in the curve (chart 21), it would seem that

TABLE 42.—*Comparison of the Groups with the Small, the Medium and the Large Diameters of the Wheal at the Site of Injection of Thyroxin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Wheal (20 Patients)	Medium Wheal (42 Patients)	Large Wheal (20 Patients)
As to Type of Tuberculosis			
Minimal	30%	28%	0
Moderately advanced	25%	30%	35%
Far advanced	45%	42%	65%
	100%	100%	100%
As to Prognosis			
Good	50%	45%	5%
Fair	25%	28%	45%
Poor	25%	26%	50%
	100%	100%	100%
As to Weight Curve			
Gaining	25%	45%	55%
Stationary	55%	42%	20%
Losing	30%	13%	25%
	100%	100%	100%

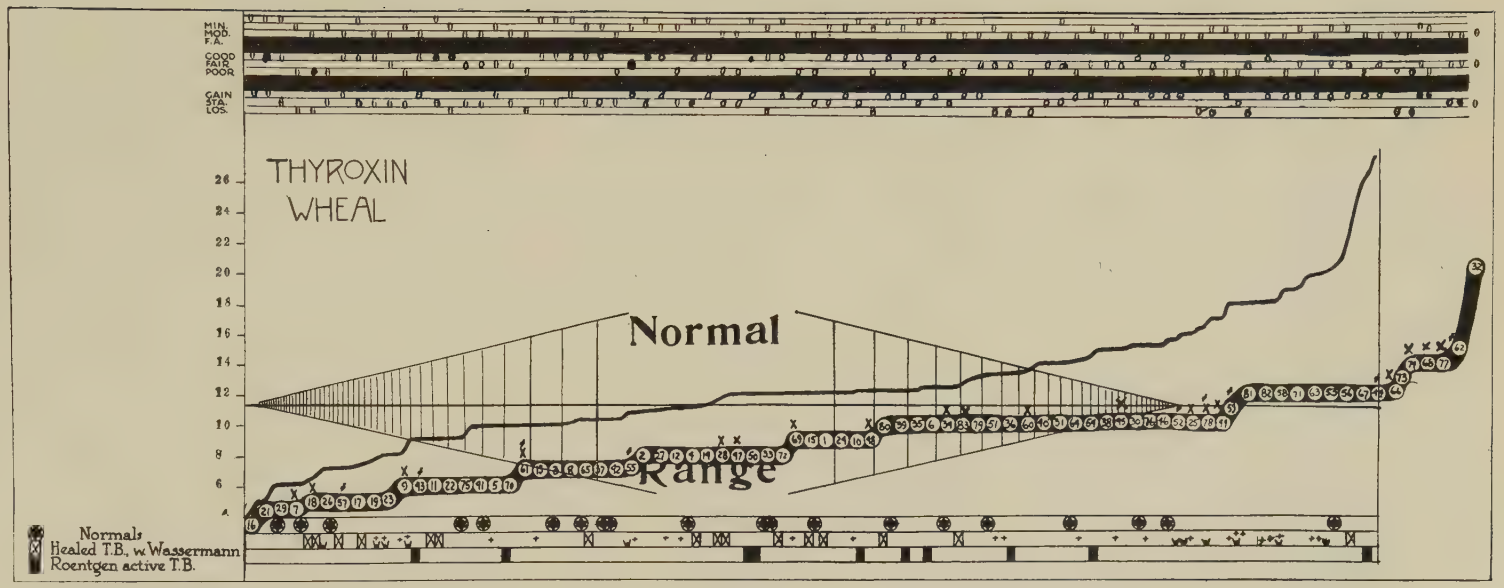

Chart 21.—The curve of the intracutaneous reaction to thyroxin (wheal).

there are more cases of far advanced tuberculosis in the group with the larger wheals, that the prognosis is best in the group with the small wheals, and that the gain in weight seems to be most favorable in the groups at the intermediate and upper portions of the curve.

When we examine table 43, in which the groups at the extreme ends of the curve are compared in detail, we note that the flare at the site of the injection of thyroxin is largest in the group with the small wheals, in whom also the capillary permeability is somewhat increased and the value of the K/Ca ratio somewhat higher. The average protein percentage is less in the group; the ice reaction time and the salt solution absorption time are also somewhat shorter. There are nine persons with positive endothelial reactions as compared with seven in the group with larger wheals.

TABLE 43.—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Wheal at the Site of Injection of Thyroxin*

Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	Blister Time, Hours	Capillary Permeability	Inflammatory Index	Calcium Mg.	Potassium, Mg.	K/Ca Ratio	Protein, Mg.	Ice Reaction Time, Seconds	Endothelial Reaction	NaCl Absorption Time, Minutes	Deaths
5.35	3.05	7.72	67.3	9.47	10.2	19.3	1.9	8.341	9.6	11+ 9—	75.2	6
12.5	0.92	6.95	63.9	9.38	10.3	18.1	1.75	9.338	13.8	7+ 13—	85.2	7

INTRACUTANEOUS REACTION TO THYROXIN: FLARE

As twenty-nine of our patients showed no flare at the site of the injection of thyroxin, they have been grouped together, and the rest of the material has been divided into a group showing a small flare and a group showing a large flare of twenty-seven and twenty-six patients, respectively.

From the curve in chart 22, it will be observed that the flare in the tuberculous group is less marked than in the "normal" and miscellaneous clinical groups previously examined, and that the deaths, as well as the cases with pleural effusion, are uniformly distributed. Table 44 indicates that there is no correlation of the size of the flare with the clinical status. The averages of the other determinations for the groups with the smallest and the largest flares show no striking differences and we have therefore omitted the tables.

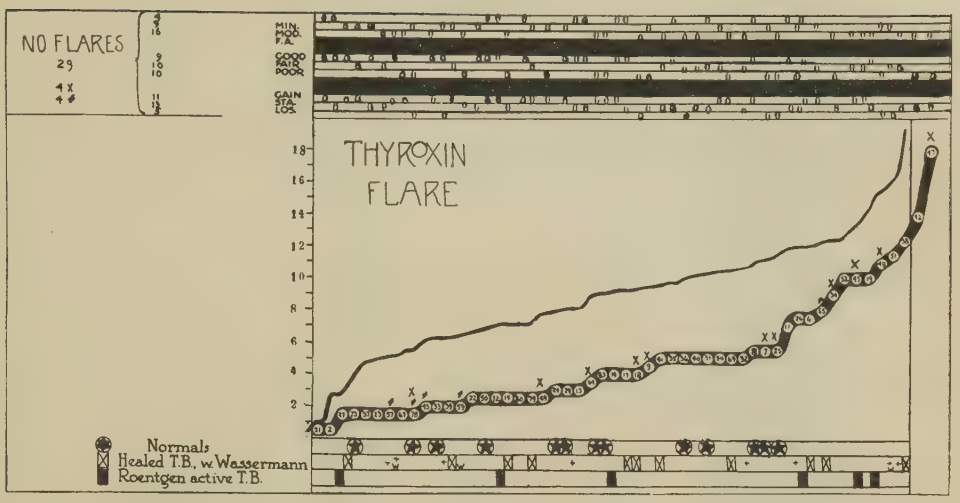

Chart 22.—The curve of the intracutaneous reaction to thyroxin (flare).

TABLE 44.—*Comparison of the Groups with the Small, the Medium and the Large Radii of the Flare at the Site of Injection of Thyroxin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Flare (29 Patients)	Medium Flare (27 Patients)	Large Flare (26 Patients)
As to Type of Tuberculosis			
Minimal	13%	33%	20%
Moderately advanced	31%	37%	27%
Far advanced	56%	30%	53%
	100%	100%	100%
As to Prognosis			
Good	30%	60%	20%
Fair	34%	14%	42%
Poor	36%	26%	38%
	100%	100%	100%
As to Weight Curve			
Gaining	37%	60%	27%
Stationary	45%	30%	50%
Losing	18%	10%	23%
	100%	100%	100%

REACTION TO TUBERCULIN [18] (TWENTY-FOUR HOURS)

The size of the reaction at the site of the injection of tuberculin, as measured after twenty-four hours, varied in our series from 0 to 28.5 mm. The curve in chart 23 illustrates the series. If we divide the group into those with negative or small, those with intermediate and

18. Long's Synthetic Tuberculin used.

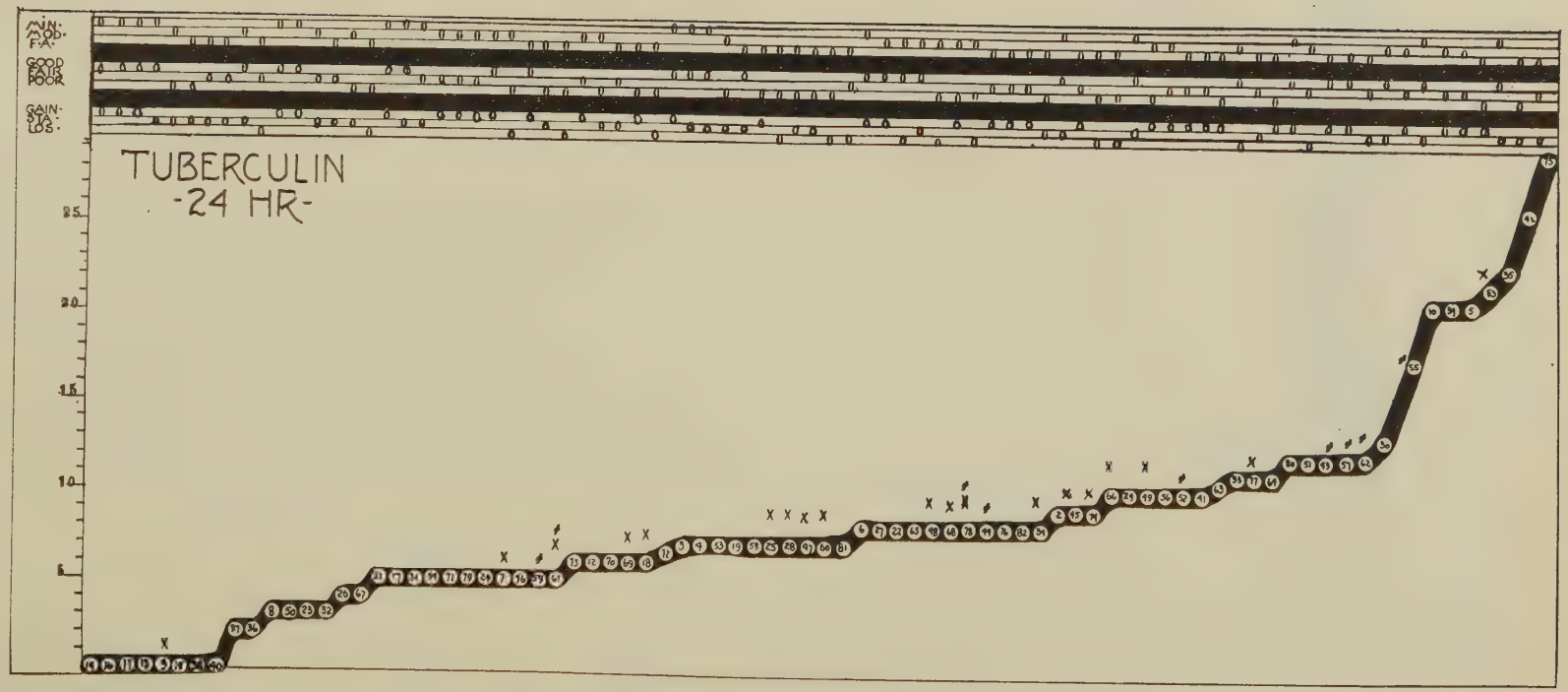

Chart 23.—The curve of the reaction to tuberculin (at twenty-four hours).

those with large reactions, we find that there are more cases of minimal manifestation in the group with small reactions and more cases of far advanced tuberculosis in the group with large reactions. There appears to be absolutely no difference in the clinical prognosis as between these groups and no clearcut difference as far as the weight curve is concerned. It will also be observed that the deaths are distributed largely in the center of the curve and that the cases with pleural effusion seem to be associated with somewhat larger flares.

TABLE 45.—*Comparison of the Groups with the Small, the Medium and the Large Diameters of the Reaction at the Site of Injection of Tuberculin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Wheal (24 Hours) (20 Patients)	Medium Wheal (24 Hours) (41 Patients)	Large Wheal (24 Hours) (20 Patients)
As to Type of Tuberculosis			
Minimal	45%	14%	15%
Moderately advanced	25%	36%	30%
Far advanced	40%	50%	55%
	100%	100%	100%
As to Prognosis			
Good	45%	29%	35%
Fair	35%	24%	45%
Poor	20%	47%	20%
	100%	100%	100%
As to Weight Curve			
Gaining	35%	41%	55%
Stationary	55%	31%	35%
Losing	10%	28%	10%
	100%	100%	100%

In table 46, in which the groups at the extreme ends of the curve are compared, it may be noted that in the low group there is more potassium and less cholesterol and a smaller wheal at the site of the injection of thyroxin, but a flare somewhat larger. The salt solution absorption time is less, but the value of the corpuscles/plasma ratio is somewhat increased.

REACTION TO TUBERCULIN (PERSISTENT)

When we now take into consideration the persistency of the reaction (chart 24), we again find that there is no direct relation to the deaths. The relation to clinical status is shown in table 47. Again, the patients with the persistent and most marked flares (upper end of the curve) show a preponderance of cases of far advanced tuberculosis; there is apparently little difference between the groups as to prognosis, and the weight curve is most favorable at the end representing the most persistent and largest reactions.

TABLE 46.—*Comparison of the Results of the Examinations of the Groups with the Smallest and the Largest Diameters of the Reaction at the Site of Injection of Tuberculin*

Reaction to Tuberculin, Mm.	Blister Time, Hours	Capillary Permeability	Calcium, Mg. per 100 Cc.	Potassium, Mg.	K/Ca Ratio	Protein, Mg.	Cholesterol, Mg.	Reaction to Thyroxin, Wheal, Mm.	Reaction to Thyroxin, Flare, Mm.	NaCl Absorption Time, Minutes	Corpuscles/Plasma Ratio	CO_2 Combining Power	Deaths
2.2	7.7	67	10.3	20.2	1.96	8.3	185	8.1	4.1	65	41.3	56.3	3
14.7	7	67	10.2	18.7	1.84	8.992	207	9.3	2.9	90	38.7	55.6	3

TABLE 47.—*Comparison of the Groups with the Persistent Small, Persistent Medium and Persistent Large Reaction at the Site of Injection of Tuberculin, with Regard to Clinical Status*

Clinical Classification of Patients	Small Reaction (20 Patients)	Medium Reaction (42 Patients)	Large Reaction (20 Patients)
As to Type of Tuberculosis			
Minimal	30%	14%	30%
Moderately advanced	40%	43%	5%
Far advanced	30%	43%	65%
	100%	100%	100%
As to Prognosis			
Good	40%	31%	45%
Fair	25%	35%	25%
Poor	35%	34%	30%
	100%	100%	100%
As to Weight Curve			
Gaining	20%	50%	45%
Stationary	65%	31%	40%
Losing	15%	19%	10%
	100%	100%	100%

TABLE 48.—*Comparison of the Groups with the Negative, the Medium and the Marked Tuberculosis Complement Fixation, with Regard to Clinical Status*

Clinical Classification of Patients	Negative Fixation (20 Patients)	Medium Fixation (37 Patients)	High Fixation (20 Patients)
As to Type of Tuberculosis			
Minimal	50%	16%	0
Moderately advanced	30%	30%	40%
Far advanced	20%	54%	60%
	100%	100%	100%
As to Prognosis			
Good	55%	40%	5%
Fair	15%	32%	45%
Poor	30%	28%	50%
	100%	100%	100%
As to Weight Curve			
Gaining	30%	48%	40%
Stationary	55%	35%	30%
Losing	15%	17%	30%
	100%	100%	100%

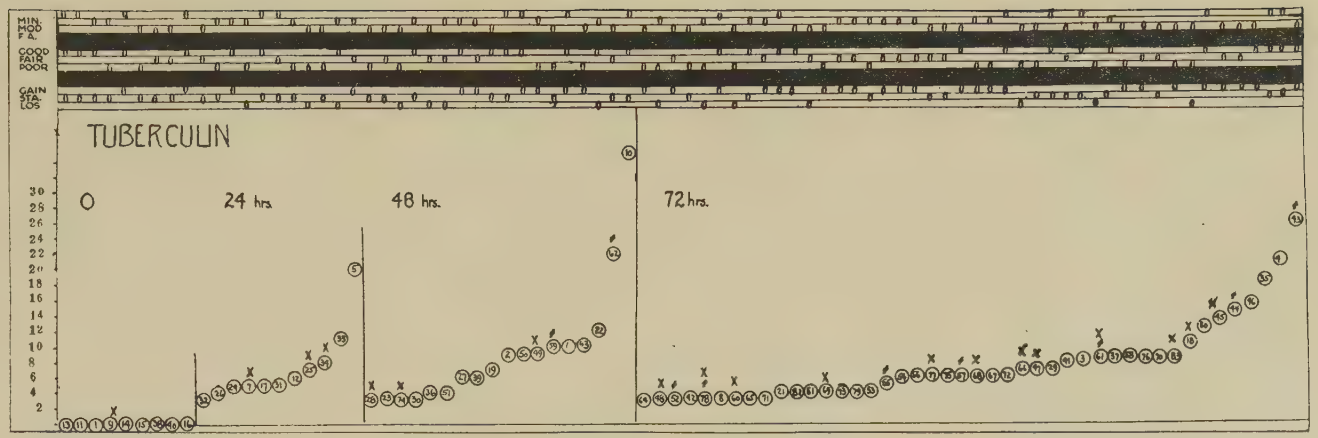

Chart 24.—The curve of the reaction to tuberculin (persistent).

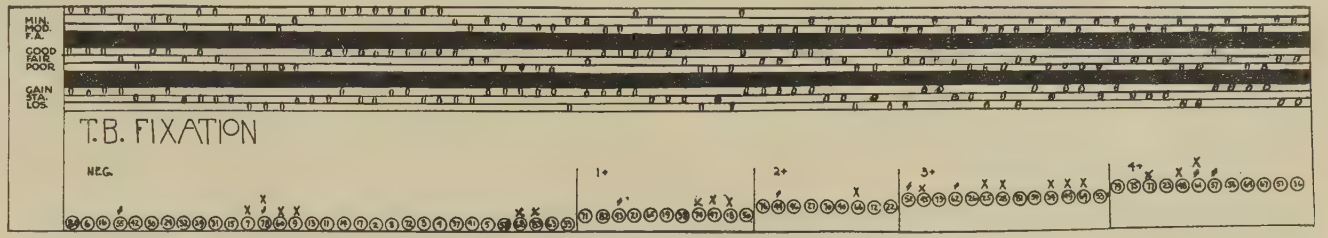

Chart 25.—The curve of tuberculosis complement fixation.

TUBERCULOSIS COMPLEMENT FIXATION

As the complement fixation reaction so largely follows the globulin and Darányi reactions, we have prepared only a curve (chart 25) of the material, and have not made tables of the results of the examinations of the patients at the extreme ends of the curve. When we classify our material on the basis of this reaction, we find that the group with the negative reactions contains more cases of minimal manifestation, and the group with the most marked reactions, only cases of moderately advanced and far advanced tuberculosis. The prognosis is best in the low group and becomes increasingly poor as we proceed to the group with more marked reactions. There is no apparent relation to the weight curve.

C. CLINICAL STUDY OF ALTERATIONS IN THE PERMEABILITY OF THE CAPILLARIES IN PATIENTS WITH TUBERCULOSIS

The material presented here makes it apparent, we believe, that so far as the patient with pulmonary tuberculosis is concerned, increased inflammatory reactivity is usually associated with increased clinical activity. With lessened constitutional reactivity, the clinical course is relatively benign. It is self-evident that one must keep in mind the many exceptions, the fact that the tuberculous lesion may be cured by absorption, that many of our forms of therapy make use of stimulation, etc.

Practically, our therapy consists in the effort to support normal and inherent forces of resistance either by insuring rest and proper food or by recourse to methods of moderate stimulation by physical agents.

Theoretically, three major lines of therapeutic approach to the problem of tuberculosis can be discerned. There is first and foremost the field of specific immunity, with the attack directed toward the virus; of late, the cellular aspect of the problem is receiving more attention. The second is fundamentally chemotherapeutic in the specific sense of Ehrlich. Here, again, it is the specific destruction of the virus that is the immediate goal, the reaction of the tissue being considered only to the degree that the agent shall not of itself be too toxic. Even this apparently straight line of attack is being seriously questioned, and modern investigators (the recent paper of Seifert,[1] for instance) would now place much greater emphasis on the reactions of the tissue to the injection of the so-called specific therapeutic agent. Finally, a third line of approach takes cognizance of the reaction of the tissue, with the endeavor directed toward promoting beneficial reactions and suppressing unfavorable ones. Perhaps the enzymatic destruction of bacteria, a

1. Seifert, W.: Klin. Wchnschr. **7**:1497, 1928.

field of endeavor that has occupied Russian investigators chiefly, should be mentioned. A recent paper of Platonov [2] is one of a group that deals with a possible therapy along these lines.

We do not wish to enter into a theoretical discussion of any length in this part of the work, but we should like to emphasize the third method of therapeutic approach, namely, the endeavor to change the reaction of the host toward the infection. In this problem, the question of the capillary permeability (to proteins, etc.) immediately comes to the foreground and it is only this phase that we wish to discuss at this time. Four premises are to be taken into consideration.

1. Schade [3] recently determined that the reaction of tuberculous tissue is toward the acid side (p_H of 6.5) exactly at the optimum for the growth of tubercle bacilli. The capillaries normally respond to an acid reaction by dilatation and increased permeability.

2. The autonomic nervous system, as part of the general vegetative balance is obviously involved. Not only have the studies of Guth,[4] Glaser [5] and others made this probable, but the pioneer work of Pottenger in this country in relation to symptomatology emphasized it. Unfortunately, conflicting concepts and terminology have obscured the work in this field. Epinephrine makes the capillary endothelium less permeable. It is, however, the representative agent for producing sympathetic effects. The "sympatheticotonic" person, on the other hand, has more permeable capillaries and the blood pressure may be low. We think of the state of tissues with contracted vessels and less permeable capillaries as the typical rest stage. Yet in many persons the injection of epinephrine hydrochloride lowers the blood pressure and increases the permeability. The so-called "vagotonic" person usualy has a higher blood pressure, a lower metabolic rate and less permeable capillaries. Yet stimulation of so-called parasympathetic nerves commonly results in dilatation of the vessels and increased permeability, i. e., tissue activity. Obviously, much of the confusion results from the transfer of strictly anatomic concepts and terms to the autonomic nervous apparatus, instead of starting out on a purely functional basis (see the discussion of Kraus' concept). Relatively impermeable capillaries (an effect of epinephrine and pituitary?) are usually found associated with relatively chronic tuberculosis, and greater permeability with active tuberculosis (effect of thyroid?).

3. Even specific agents (tuberculin, sodium aurothiosulphate, sodium cinnamate, etc.) act on the capillaries, usually rendering them

2. Platonov, G.: J. Infect. Dis. **14**:549, 1926.
3. Schade, H.: Ztschr. f. d. ges. exper. Med. **49**:334, 1926.
4. Guth, E.: Beitr. z. Klin. d. Tuberk. **60**:39, 1924.
5. Glaser, W.: Beitr. z. Klin. d. Tuberk. **55**:390, 1923.

more permeable for a time, and later diminishing their permeability. The focal reaction, whether in the form that is obvious clinically, or consisting merely of practically imperceptible biologic reactions following in the wake of minute doses of various agents, is a reaction that depends on changes in the permeability of the capillaries about the focus.[6]

4. Various biologic influences (endogenous or exogenous), among them menstruation, the effect of the season, etc., which are distinctly associated with increased permeability and autonomic instability are frequently found associated with distinct clinical evidences of activation.

The conclusion might seem warranted that increase in capillary permeability, however produced, unfavorably influences a tuberculous process.

METHODS OF DIMINISHING PERMEABILITY

Granted these simple premises, how can one proceed to bring about diminished permeability of the tissues? Several possibilities may be considered:

1. Alkalinization.
2. Agents acting directly on cell membranes, chiefly epinephrine and pituitary (perhaps insulin).
3. Increasing the calcium of the plasma.
4. Diminishing the activity of the thyroid or of the sex glands.
5. Producing a peripheral regional (skin and muscles) autonomic stimulus with resulting compensation in the visceral area.

Alkalinization.—In its general effects alkalinization must make tissues less permeable, for the converse, local acidosis, makes the capillaries dilate and the endothelial cells more permeable. Modrakowski and Lentz have recently confirmed this.[6a] It must be kept in mind that with the usual methods at one's disposal, alterations produced by therapeutic measures (administration of citrates, the Sippy diet, etc.) are never pronounced and, at best, the CO_2 combining power is increased to only a minor degree. Jordan's work[7] indicates that there may be considerable difference in the effect, however, in different persons.

Epinephrine and Pituitary.—Both epinephrine and pituitary diminish the permeability of cells, even in high dilution. Langer[8] demonstrated this effect for epinephrine and we showed the same effect for

6. Levinson, S. A., and Petersen, W. F.: Am. Rev. Tuberc. **15**:6, 1927.

6a. Modrakowski, G., and Lentz, R.: Abstracts, International Physiological Congress, Boston, 1929, p. 184.

7. Jordan, S. M.: Calcium Chloride and Carbon Dioxide Content of Venous Blood in Cases of Gastroduodenal Ulcer Treated with Alkalis, J. A. M. A. **87**: 1906 (Dec. 4) 1926.

8. Langer: Ztschr. f. physiol. Chem. **118**:1, 50 and 96, 1922.

both epinephrine and pituitary [9] in our experiments on lymph. The former has the disadvantage that it has so marked an effect on sympathetic nerve endings, increases the metabolic rate and, particularly in the tuberculous, may result in paradoxic effects. Dextro-epinephrine might obviate some of these defects. Pituitary seems to act well when injected in slowly absorbable form. It has the additional advantage that its effect is apparent even on irritated capillaries, when epinephrine fails. As the effect of these agents on capillary permeability is of considerable interest, we have performed an experiment in a dog, in which epinephrine (1 mg.) and pituitary in oil (dosage corre-

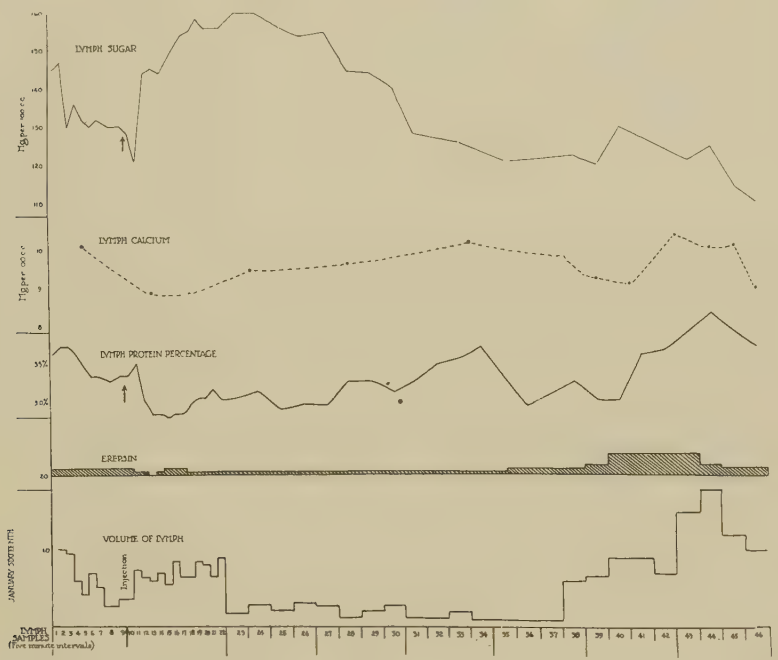

Chart 1.—Effect of injection of epinephrine and pituitrin on lymph volume, lymph concentration, lymph sugar, lymph calcium and erepsin.

sponding to one therapeutic dose in man) were given intramuscularly. The long continued diminution of the lymph flow after the primary increase due to increased blood pressure and the diminution in the concentration of protein indicate the change in permeability. The lowering of the calcium of the lymph is in line with this change.

Calcium.—The value of the administration of calcium is problematic. The fault is not necessarily in a deficiency of calcium in the fluids, but in the fact that calcium, because of the vegetative status, is not fixed by the cells. The mere increase of the calcium of the plasma

9. Petersen, W. F., and Hughes, T. P.: J. Biol. Chem. **66**:229, 1925.

produced by the administration of calcium can have little effect, nor will the use of parathyroid hormone be of avail (as recently demonstrated by Gordon, Roark and Lewis,[10]) because in that case one is merely taking calcium from tissue reserves to increase it in the fluids of the body. Nevertheless, it may be useful in cases in which a relatively low calcium level can be demonstrated in the plasma and the tissues are able to fix the excessive calcium offered them.

Diminution of the Activity of the Sex Glands and of the Thyroid Gland.—Diminution of the activity of the sex gland in women is of obvious therapeutic importance, not only with the idea of sterilization and the avoidance of pregnancy, but on the basis that menstruating tuberculous women are more apt to have activation of the tuberculous process. The effect of thyroid activity is less apparent and still problematic. Coulaoud [11] described an activation of tuberculosis following the administration of thyroid extract. On general principles, lowering of the metabolic rate might be useful in cases in which one is already dealing with an increase due to the infection. The relative benignancy of tuberculosis in castrated animals and man has been established.

Therapeutically, measures designed toward the reduction of such endocrine activity are available. In the female, at least, a transient or permanent sterilization by means of the roentgen ray is easily carried out.

Finally, we must consider the production of a peripherally localized autonomic disturbance. In a series of papers, Müller and one of us (W.F.P.) [12] demonstrated the close autonomic interrelation of the splanchnic area and the peripheral (skin and muscles) region. Stimulation of the one (parasympathetic status) is promptly followed by sympathetic orientation in the other area. Thus, if the skin is made parasympathetic by stimulation (a burn, an intracutaneous injection, etc.) the splanchnic area becomes sympathetic in its general tonus. If, for instance, one wishes to alter the vascular status of a peritoneal tuberculosis, this may be done by producing a superficial effect on the skin. As a matter of fact, this has been suggested empirically in the treatment of tuberculous peritonitis, an ultraviolet burn of an area approximately 10 by 10 cm. being used.

One has, then, a series of measures available which, either singly or in combination, might influence the general reaction of the tuberculous person by altering the rate of absorption of toxic material from the foci of the disease.

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10. Gordon, B.; Roark, J. L., and Lewis, A. K.: Effect of Parathyroid Hormone on Certain Signs and Symptoms in Tuberculosis, J. A. M. A. **86**:1683 (May 29) 1926.

11. Coulaoud, E.: Médecine **3**:627, 1923.

12. Müller, E. F., and Petersen, W. F.: Klin. Wchnschr. **5**:1025, 1926.

May one at the same time make the soil less favorable for the growth of the organism? This is a question that only long experience and experimentation will solve. The presumptive evidence is in favor of this view, and for the following reasons: The reaction at which the tubercle bacilli seem to grow best in the human organism is at a p_H of 6.7, i.e., slightly on the acid side of neutrality. This is the range at which Schade found the caseous material of the tubercle. If one is able to alkalinize the tissues or to create a tendency toward restoration to the alkaline side, the soil might, it seems, be made less favorable.

CLINICAL OBSERVATIONS:

THE INJURIOUS EFFECT OF INCREASE IN PERMEABILITY

The first two cases concern twin sisters, 23 years of age. Both had been under observation at the municipal dispensaries for a long time and for a short time were at the Municipal Sanitarium.

Clinical History of Sister A.—The illness began with pleurisy in 1920; in 1922, there was cough with loss of 20 pounds (9 Kg.), night sweats, etc. In addition, the patient had numbness and twitching of the right arm, with some plasticity, and later of the entire right side, but this had gradually lessened. She had several convulsive seizures in February, 1924. The family history was negative. On examination, it was noted that the right shoulder drooped, and that there was marked degeneration of the subcutaneous tissues of the right arm, which was paralyzed. The condition of the lungs indicated a far advanced "C" (Turban III, right IV, left III). The temperature was 101 F. in the afternoon; the pulse rate was 120. Tubercle bacilli were found in the sputum. The urine was normal. The Wassermann reaction was negative. The tuberculosis complement fixation was ++. The hemoglobin content was 70 per cent. The red cell count was 4,750,000, and the leukocytes numbered 11,300.

The patient entered the Research and Educational Hospital in June, 1925, with essentially the same physical conditions. The roentgenogram revealed cavitation of both upper lobes and an extensive parenchymal infiltration throughout both lungs.

The infection, as determined by further investigation, probably had occurred during childhood by transmission from a seamstress who frequently worked and lived in the family. She had had an apparently active tuberculosis, and the twin sisters frequently had been in contact with her for considerable periods.

On admission, the weight of patient A was 76 pounds (34.5 Kg.). In the graphic chart of this patient (chart 2) it may be noted that the temperature and the pulse rate during the control period of observation fluctuated within a constant range. On July 4, the patient was inadvertently exposed to rather intense sunlight for several hours, and an activation was immediately apparent, the average of the maximal temperatures increasing 0.7 F.

On July 13, 15 and 17, the patient was given 2 mg. of pilocarpine in oil (intramuscular injections). Despite the fact that peripheral dilatation should be followed by a decrease in temperature, there was a marked increase both of temperature and of pulse rate (chart 2). Two weeks after the first injection of pilocarpine, the patient began to complain of severe headache; the temperature

increased markedly, delirium developed thirty-three days after the injection, and one week later the patient died with all the clinical and laboratory evidences of tuberculous meningitis.

It may be of interest to observe in chart 2 that intramuscular injections of epinephrine in oil were given the patient after the onset of the tuberculous meningitis and a striking effect on the basal metabolic rate was noted. So, too, the injection of large doses of dextro-epinephrine (5 mg. in oil on alternate days) may have influenced the temperature for a short period before death.

Autopsy (by Dr. R. H. Jaffé).—The body was that of a fairly well-built, extremely emaciated female. The skin was pale yellow-gray with several livid patches on the back. The subcutaneous fat was reduced to a yellow-brown layer, from 3 to 5 mm. thick.

The lungs were adherent to the thoracic wall by a fibrous band, especially in the upper lobes. The lower margins of the lower lobes were distended and rounded off. The posterior part of the right upper lobe contained a large irregular cavity from 2 to 3 cm. in diameter, filled with a small amount of yellow-green fluid. The walls were smooth and gray-red. Elevations corresponding to the larger vessels were present. The cavity communicated with the larger bronchi of the upper lobe. There were groups of acinose yellow-gray nodules in the center of the right lower lobe. The left lung showed an irregular cavity in the posterior part of the upper side of the lower lobe. It was 0.5 cm. in diameter and its walls were similar to those of the cavity described. About this cavity in the left lung were several small yellow nodules in areas of gray-red consolidation. Near the base of the left lower lobe was a small, round cavity with smooth, gray-white fibrinous walls, about 9 mm. in diameter. Attached to this cavity was a small, fibrous, calcified nodule with branches of scar tissue about it. The lymph glands of the hilum about the tracheal bifurcation were slightly enlarged, gray-red and soft.

The heart weighed 175 Gm. The pericardial cavity contained 100 cc. of clear, yellow fluid. The left ventricular wall was 12 mm. in diameter. The right ventricular wall was 4 mm. in diameter. The myocardium was red-brown and soft. The endocardium of the left ventricle showed a whitish thickening over the septum. There were no changes in the valves. The aortic circumference above the valves was 58 mm. Small yellow elevations about the coronary openings were found. Large, yellow-white plaques were found in the ramus ascendens of the left coronary artery.

The spleen weighed 88 Gm. It was soft and dark red, and the cut surface showed distinct structure.

The liver weighed 905 Gm. The surface was smooth and gray-brown, with irregular yellow patches on the convexity of the right lobe. These patches extended about 1 cm. into the liver tissue. The cut surface showed almost no structure.

The suprarenal glands showed the cortex gray-white, with yellow nodules, and the medulla deep brown.

The kidneys weighed, left, 135 Gm., right, 110 Gm. The capsules stripped easily. The surface of the left kidney showed distinct fetal lobulation. The cortex was gray-red, the medulla dark red.

The stomach contained a small amount of gray fluid. The mucosa had been destroyed by postmortem changes.

The cecum contained several round, superficial ulcerations from 3 to 5 mm. in diameter. The edges were notched. The mucosa was dark red; no changes appeared in the other parts of the intestine.

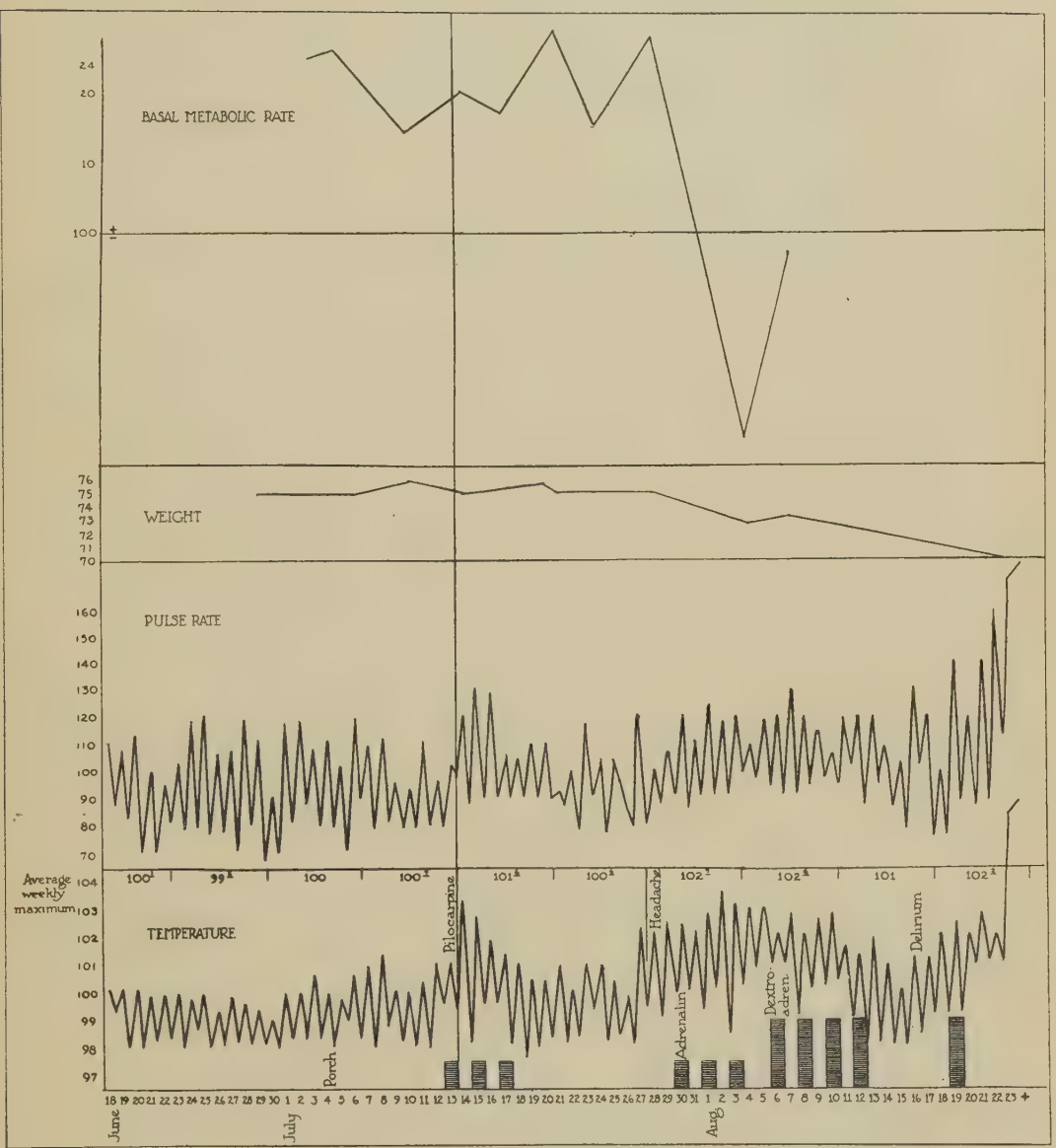

Chart 2.—Clinical record of sister A, who died from tuberculous meningitis. The patient was treated with pilocarpine and epinephrine.

The ovaries were small with deep depressions on the surface. They contained no corpora lutea. There was a small cyst in the right ovary.

The uterus was small. The mucosa was anemic.

The pancreas weighed 72 Gm. It was about 17 cm. long. The color was gray-red.

The dura mater was smooth and gray-white. Dark red blood clots were observed in the longitudinal sinus.

The brain was swollen. The convolutions were flat; the leptomeninges over the convexities were deep red. Over the base of the brain was a large amount of yellow-green, gelatinous exudate, covering the pons and filling the space about the infundibulum. Many small, gray nodules occurred along the arteria cerebri media and diffuse nodules occurred near the pole of the temporal lobe. The ventricles were distended and filled with a cloudy, gray-red fluid. The brain tissue was soft. A small thickening was observed in the meninges near the median edge of the left convexity over the upper part of the anterior central convolution. Incisions here revealed a small yellow nodule from about 3 to 5 mm. in diameter, lying between the gray and the white matter. The nodule stood out, separated from the surrounding tissue by a fine gray line.

Anatomic Diagnosis.—The diagnosis included the following conditions: large tuberculous cavities in the right upper and left lower lobes, fresh acinose eruptions in the center of the right lower lobe, submiliary tubercles in the surroundings of the cavity in the left lower lobe and an encapsulated tubercular lesion in the basal part of the left lower lobe; tuberculous meningitis; acute edema and hydrocephalus internus of the brain and old solitary tubercle in the anterior central gyrus of the left convolution; fresh tuberculous ulcers of the cecum; atrophy of the heart; cloudy swelling, edema and incipient cloudy degeneration of the liver; cloudy swelling of the kidneys and atrophy of the spleen.

Histologic Observations (Dr. Jaffé).—Spleen: Many miliary tubercles were present in the pulp. They consisted of epithelioid cells and single large giant cells.

Lungs: In the surroundings of the tuberculous cavities many acinar tubercles were found in the thickened interalveolar septums. These tubercles showed much caseation. Collagenous fibers extended between the epithelial cells of the marginal zone into the caseated centers, where they were distinguished between the tuberculous débris. Much fibrous tissue surrounded and separated the tubercles.

Brain: The nodule in the cortex of the left convexity of the brain consisted of a cheesy center, surrounded by a well of large, round, foamy cells and lymphocytes. Between these, distended capillaries were visible. Outside the cellular zone was a capsule of dense collagenous connective tissue, stained bright red in the van Gieson sections. About this capsule was a marked proliferation of glia tissue. Distended blood-filled capillaries perforated the fibrous capsule.

Kidney: The kidneys showed little change: a diffuse capillary hyperemia of the medulla and a slight swelling of the epithelium of the convoluted tubules.

Liver: There were few submiliary tubercles. They consisted of one or two giant cells, a group of lymphocytes and a thick capsule of hyaline connective tissue, which extended into the center of the nodules.

The heart revealed marked pigmentation of the myocardial fibers. The suprarenal glands showed the lipoid content of the cortex much diminished, and hyperemia of the reticulum. No changes were noted in the pancreas.

THE CONVERSE

We turn now to the converse of this picture.

Clinical History of Sister B.—The twin sister B entered the Municipal Sanitarium with patient A (July, 1924). She gave a history of pleuritic pains, abdominal pain, loss of 20 pounds (9 Kg.), and cough, which had been present for a year. In February, 1924, she had an acute exacerbation, with chills and sweats, and was in bed for ten weeks.

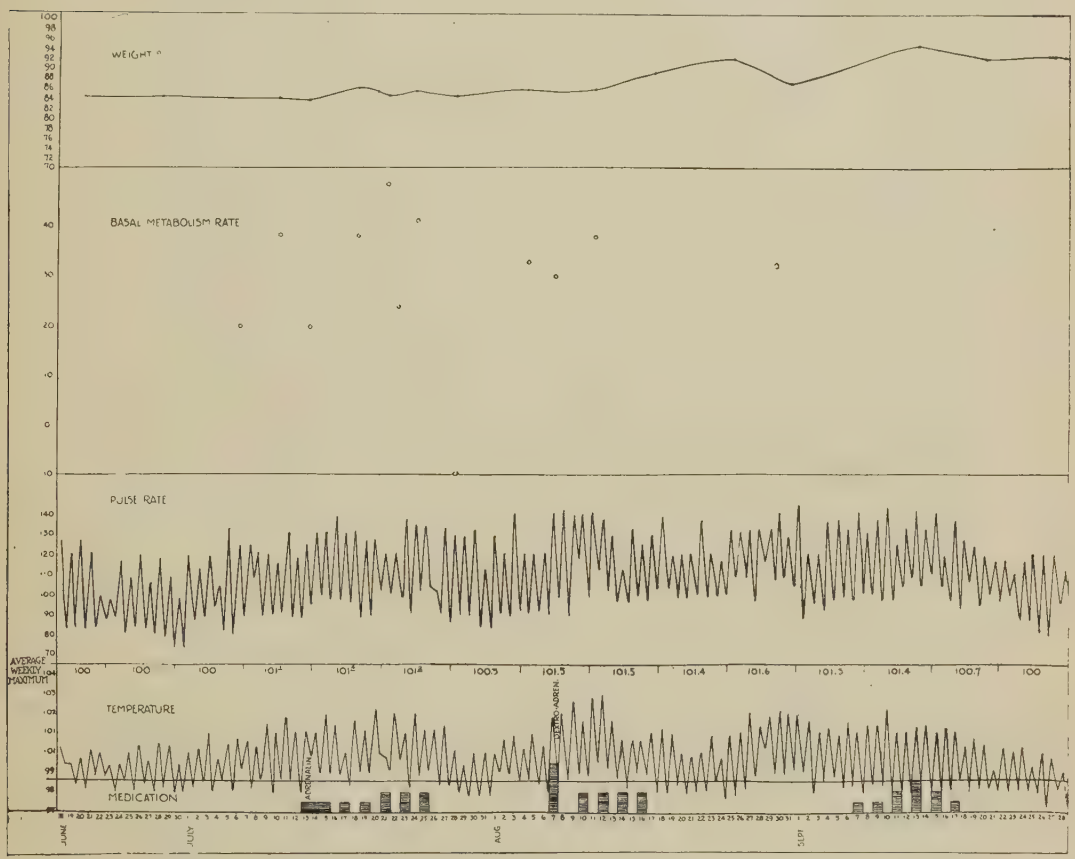

Chart 3.—Clinical record of sister B, who improved on injection of epinephrine.

The examination made when she entered the sanitarium revealed a pulmonary involvement classified as far advanced "B" (Turban III, left III, right II). The sputum was negative; the Wassermann reaction was negative; the tuberculosis complement fixation was +; the hemoglobin content was 75 per cent; the red blood corpuscles numbered 4,050,000 and the leukocytes 11,000 per cubic millimeter. The morning temperature was recorded as 96.4 F. and the pulse rate 100.

The patient was admitted to the Research and Educational Hospital on June 18, 1924, with her twin sister and was observed under identical conditions. The physical examination at admission revealed cavitation in both upper lobes and

soft parenchymal infiltrations throughout both lungs. The weight was 86 pounds (3.9 Kg.), i. e., 11 pounds (5 Kg.) more than her twin sister's, and her general condition was correspondingly better, owing to her ability to feed herself, the sister A having paralysis of the arm. The temperature and pulse curves were practically identical.

After having been under observation for two weeks, this patient also was inadvertently exposed to sunlight for several hours on July 4 and reacted with an increased temperature, as had the sister. On July 13, 14 and 15, 1 mg. of

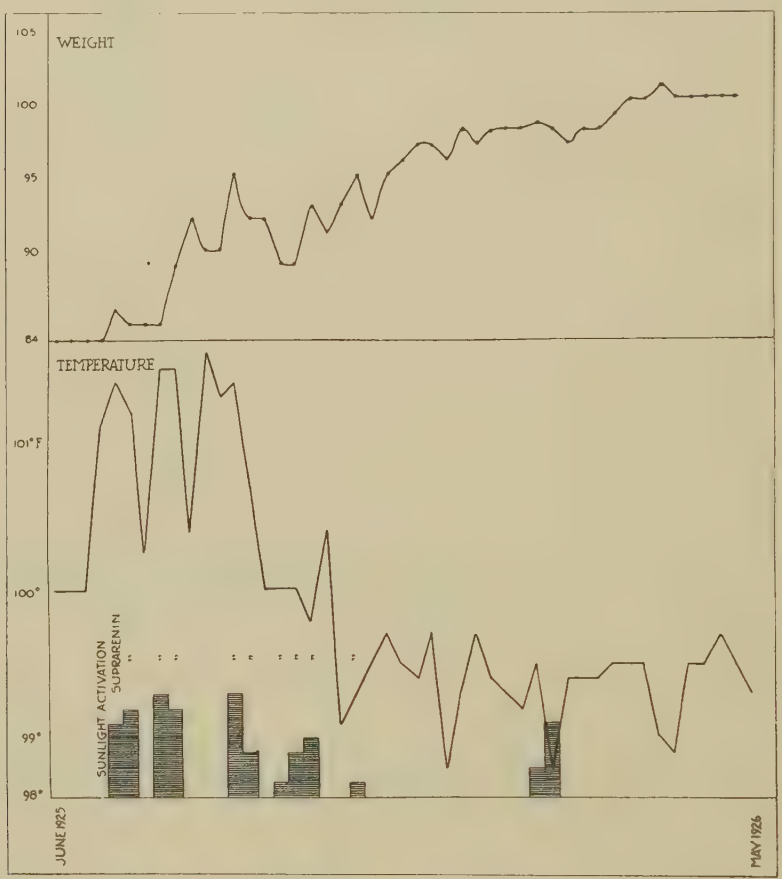

Chart 4.—Condensed chart of year's observation of sister B, showing effect of treatment with epinephrine in tuberculosis activated by an overdose of sunlight.

epinephrine bitartrate (in oil) was given intramuscularly, and similar injections were made on June 17 and 19. On June 21, 23 and 25, 2 mg. were injected and, in addition, calcium lactate was given by mouth. After this course of injections, the temperature receded for five days. The further course of the patient's illness was relatively uneventful. Repeated injections of epinephrine were made, the patient gradually increased in weight and the temperature diminished, but the pulse rate and the basal metabolic rate remained high. The patient was discharged from the hospital in May, 1926, and was still under observation at the time

of writing. She had retained her weight (105 pounds) and the tuberculous process seemed relatively stationary (charts 3 and 4).

Conclusions.—We believe that we may properly conclude that the increase in permeability induced by the pilocarpine injected (moderate dosage in oil) adversely affected the tuberculous process. It brought about increased absorption from the tuberculous foci (indicated by the increases in temperature shortly after the injections, despite the fact that the loss of temperature from the skin must have been accelerated) and with it mobilization of organisms and extension of the disease (terminal meningitis). The objection can be made that the patient was susceptible to cerebral involvement, as she had previously recovered from a solitary cortical tubercle, and that consequently the terminal meningitis represents merely a coincidence.

If increased permeability of tissue is harmful, then diminished permeability of tissue must be beneficial. This seems to be indicated in the clinical course of the twin who received injections of epinephrine. The effects on the temperature of this patient indicate a distinct improvement after each series of injections. The patient gained weight and felt stronger. We may at least conclude that in this patient the injection of epinephrine was not harmful.

It is not our intention in this paper to present clinical material from a therapeutic point of view; we wish merely to establish the experimental possibility that alterations in permeability may influence the clinical picture and that the increase in permeability that we have established as associated with increasing clinical activity may be causative of the clinical status rather than incident to it. The following case histories may be of interest in this connection:

REPORTS OF OTHER CASES

CASE 1.—A young white boy, aged 9, had been ill with Pott's disease for two years. He entered the hospital the first week in January, 1926, with a psoas abscess, which was discharging profusely. For the following three months, he remained under the observation of the orthopedic staff. During this time there was a continued loss of weight with marked anemia and a progressive increase in the temperature to a weekly maximal average of 104 F. (first part of chart 4).

Treatment was commenced on the first of April with a skin burn (Alpine lamp, abdominal exposure, twenty minutes, area 10 by 10 cm., distance 20 cm.). A second and a third exposure were made as indicated in chart 5.

In addition, epinephrine in oil was injected intramuscularly on alternating days, beginning April 9 (five injections). The injections were not continued, because the child was emaciated and the injections caused some pain. Later epinephrine was given by mouth (dosage, 5 drops three times a day).

Sodium citrate was given continuously by mouth from April 11 until the end of May (dosage, 1 Gm. three times a day).

Examination of chart 5 indicates that an improvement commenced about one week after the third period of irradiation of the skin. At about the same time, the discharge lessened and finally ceased two weeks before the patient left the hospital. It was not possible to keep the child for a long time for observation.

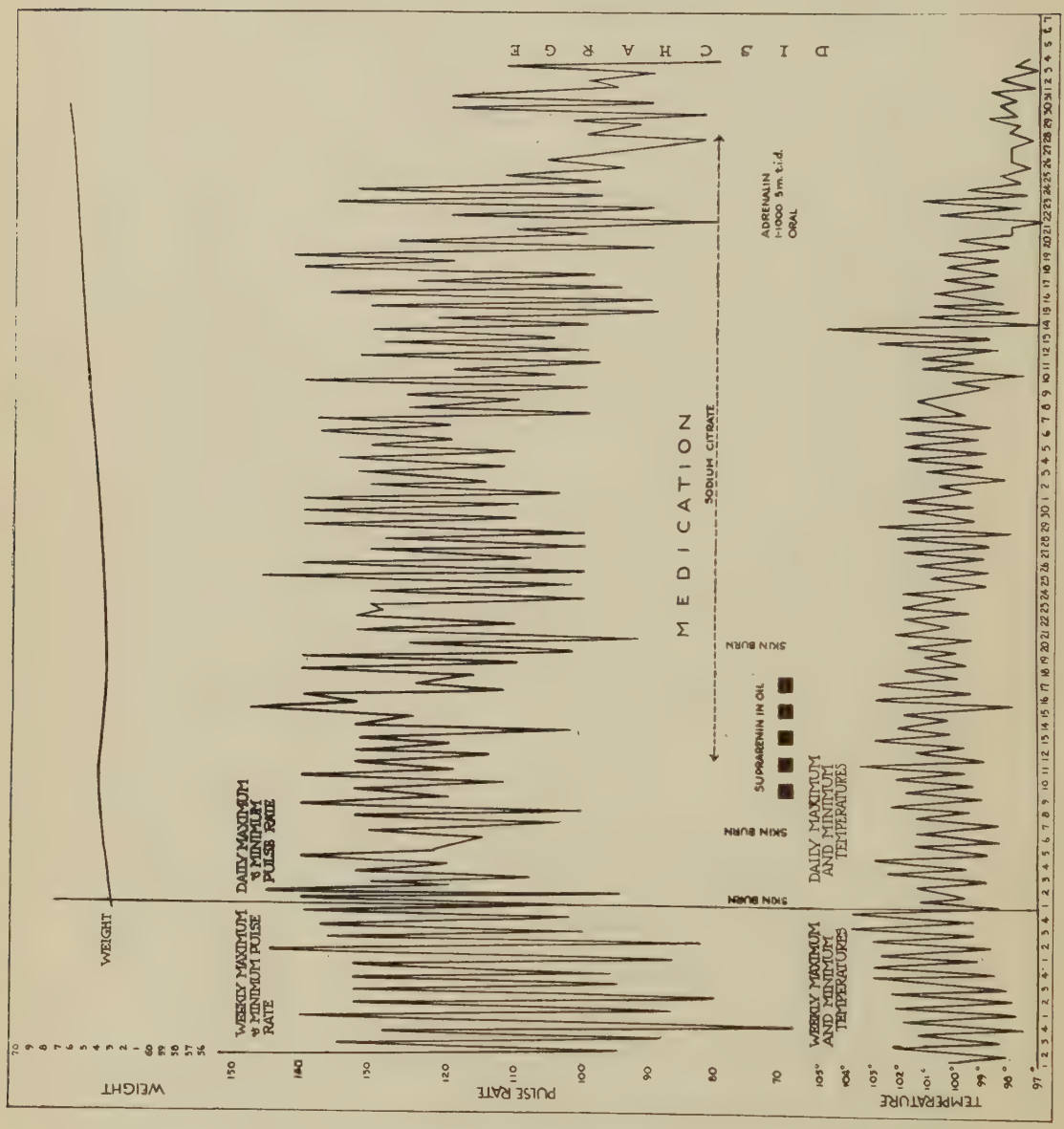

Chart 5.—Effect of treatment with skin burn (Alpine lamp), epinephrine and sodium citrate (case 1).

In this patient, rest in bed and relative immobilization resulted in no improvement during a period of observation of three months. Measures instituted with the view of diminishing capillary permeability were followed by an apparent cessation of the symptoms of activity as far as the psoas abscess and the temperature of the patient were concerned.

Case 2.—The patient had been ill for at least seven years, beginning with influenza in Germany, where she had collapse therapy of the right lung with subsequent refilling at frequent intervals. She came to America in 1924. She worked hard as a maid and had suffered a breakdown in December, 1924. She was admitted to the Cook County Hospital in December, 1924, and she remained there until Aug. 5, 1925; then she was transferred to the Research Hospital. The maximal and minimal weekly averages of temperature for her stay at the Cook County Hospital are given in chart 6, as well as the daily maximal and minimal temperatures for her stay at the Research Hospital.

Physical examination indicated a far advanced pulmonary tuberculosis with pyopneumothorax of the right side.

The pulse range after admission was somewhat higher than it had been at the Cook County Hospital. No change was made in the patient's routine of life. Ten days after her admission a daily dose of calcium lactate (3 Gm.) was given for three days. There was an immediate effect on the pulse rate, the patient coughed more and had a poor appetite, and four days later the temperature rose to 102.4 F. The sputum was not increased. The pulse rate diminished in the following ten days, but the temperature showed a tendency to increase (marked 1 in the chart).

Epinephrine in oil, in dosage of 1 mg., was now given for five successive days, together with calcium lactate. The patient responded with a marked increase in pulse rate, a rise of temperature and an increase of sputum, was nauseated, coughed more and was sleepless and tired (marked 2 in the chart).

Obviously, the patient responded at least in part vagotonically to the agents that are ordinarily considered sympatheticotonic. This is by no means uncommon. We have observed it frequently in animals receiving injections of small doses of epinephrine in oil, and it is, of course, not uncommon in patients in whom the autonomic tonus is so altered that parasympathetic overbalance exists (Guth). The patient returned to the preinjection condition about two weeks after the injections.

On September 29, 5 mg. of epinephrine in oil was given by mouth. An effect was apparent both on the pulse rate and on the temperature (the temperature had increased, however, before the ingestion. (This stage is marked 3 in chart 6.)

A definite cycle of activity took place following October 14. On October 17, the patient received a 5 per cent erythema dose of deep roentgen therapy over the noncollapsed lung. Further doses were given from October 26 to October 27, with evidences of activation following. The patient died December 13.

Anatomic Diagnosis.—Right empyema pleurae and tuberculous cavities in the upper part of the right upper lobe; collapse of the right lung; smaller cavities in the left upper and lower lobes; acinose-nodose tuberculosis of the left lung, and tuberculous bronchopneumonia in the left lower lobe.

Gross Observations at Autopsy.—The thyroid gland weighed 25 Gm. The upper respiratory tract showed large tonsils with deep grooves.

The right pleural cavity was filled with thick pus, and there was complete collapse of the right lung. A cavity, 5 cm. in diameter, was found in the apex of the right lung, communicating with the larger bronchus. There were small areas of bronchopneumonic infiltration in other parts of the right lung. Adhe-

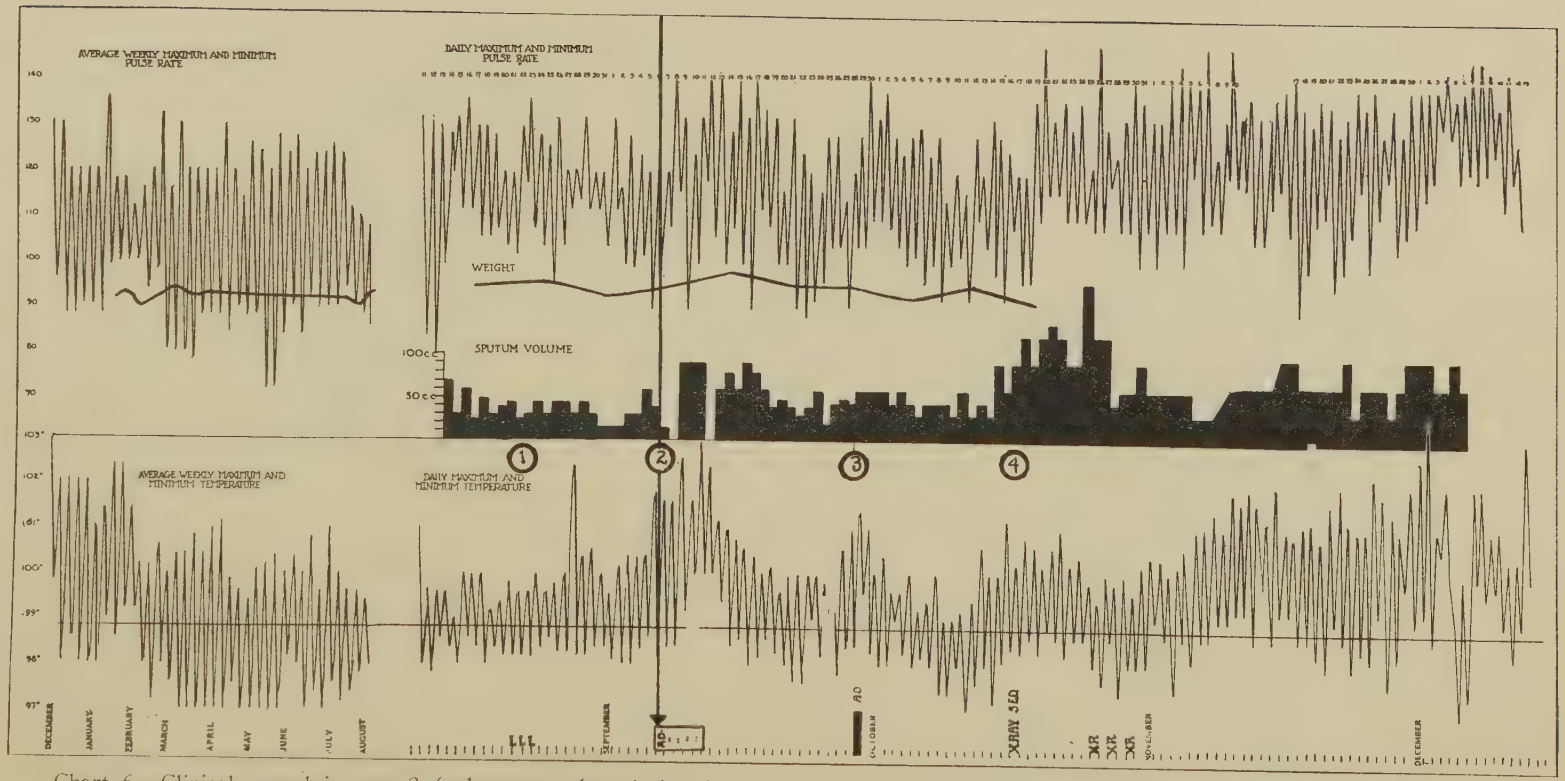

Chart 6.—Clinical record in case 2 (pulmonary tuberculosis with pyopneumothorax of the right side). The patient was treated with calcium-lactate, epinephrine and roentgen ray.

sions were observed about the upper lobe. A cavity, 2.5 cm. in diameter, was found in the upper lobe and another 1.5 cm. in diameter in the upper anterior third of the lower lobe. Acinose tuberculosis appeared in the upper lobe; bronchopneumonic areas in the lower lobe.

The heart weighed 277 Gm. The left ventricle was 12 mm. in diameter, the right ventricle, 6 mm. Small fatty plaques were noted above the aortic valve.

The stomach showed état mammelonné. The intestines showed catarrhal inflammation of the cecum with enlarged follicles, but no tuberculosis. The liver weighed 1,117 Gm. The pancreas weighed 57 Gm. and was 15 cm. long. The spleen weighed 3 Gm. and measured 12 by 3 by 6 cm. The suprarenal glands together weighed 13 Gm. There was little lipoid in the cortex, being restricted to a few yellow stripes. The right kidney weighed 140 Gm. and the left 147 Gm. The uterus measured 68 by 40 by 12 mm.

Histologic Observations.—Liver: In the central parts of the acini there was a marked dilatation of the portal capillaries with far advanced atrophy of the liver cells, which often appeared as narrow bands with granules of dark brown pigment and pyknotic nuclei. The liver cells in the periphery of the acini were large and clear, with vesicular nuclei and fine lipoid droplets. They were free from pigment. Small groups of cells contained larger fat droplets. Lipoid granules were present in the Kupffer cells. In some capillaries, an accumulation of white blood cells was found.

Spleen: The sinus was of medium width filled with blood. The malpighian bodies were small and without germinative centers; their reticulum cells were often enlarged. Few cells in the pulp contained fat granules. Fine dustlike fat was present in the capsule.

Kidney: Fine fat granules were observed in the basal parts of the epithelial cells of the proximal convoluted tubule. The cells were enlarged, bulging into the lumen. The nuclei were small and vesicular. More fat was found in the distal convoluted tubule. There was capillary hyperemia.

Heart: This organ showed capillary hyperemia, an increased amount of brown pigment about the nuclei of the muscle fibers, distinct striation of the fibers as a rule, and in a few places a granular disintegration of the fibrils.

Suprarenal Glands: There was hyperemia of the zona reticularis. The lipoid content of the cortex was distinctly reduced. Larger areas were almost free from fat.

Lung: Upper Lobe: Epithelioid cell tubercles of different size were noted, the larger ones with central caseation. Many giant cells were present. Much fibrosis was seen about the tubercles. The tissue consisted of a homogeneous, poorly stained basement substance that often appeared as blistering bands with a few flat and elongated cells filled with fat granules. Single giant cells and small groups of epithelioid cells were embedded with this scar tissue. The epithelioid cells were distinctly free from fat. So were the giant cells. Fat became visible where central caseation was present, forming a belt of droplets about the necrotic center. In the alveoli around the tuberculous infiltrations, many round cells full of fat were seen.

In using epinephrine, one obviously encounters the fact that it acts on the autonomic nervous apparatus both as a sympatheticotonic and as a vagotonic agent, and particularly in the tuberculous person the probability is rather in favor of the latter. With pituitary, one may anticipate a more certain outcome. We tried this first in combination with epinephrine as well as with a skin burn.

Case 3.—A young colored man was admitted with a clinical diagnosis of tuberculous peritonitis. The illness had begun six weeks before admission. Swelling of the abdomen had existed for approximately five weeks. The physical examination indicated a pleurisy of the left side with considerable distention of the abdomen with fluid.

After seventeen days' observation, treatment was commenced with the intramusclar injection of pituitary and epinephrine in oil. On January 20, epinephrine was given by mouth, in addition, and later more epinephrine in oil on alternating days. In addition, the patient was burned (ultraviolet dosage similar to that

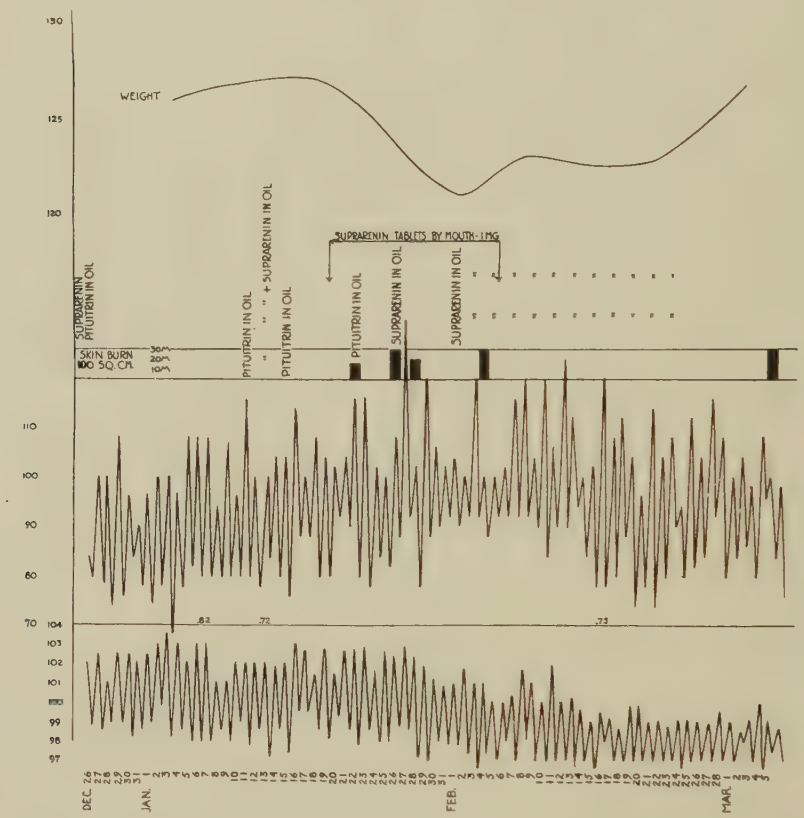

Chart 7.—Clinical record of case 3 (tuberculous peritonitis and pleurisy). Transient clinical improvement is shown.

administered to patient 1) on January 22, 26 and 28, February 4 and March 5. Being heavily pigmented, the patient was resistant to ultraviolet light. The effect of the injections of the drugs on the permeability of the skin capillaries was apparent in a reduction from 0.82 to 0.72.

Following the skin burns, the fluid was promptly absorbed from the peritoneum and the patient's weight diminished 7 pounds (3.2 Kg.). This was followed by a subsequent recovery, without reaccumulation in the peritoneum, and with no apparent further peritoneal discomfort (chart 7).

In this case the patient was by no means cured. Through a misunderstanding, the patient was discharged. He was readmitted April 1, this time with great distention of the abdomen. Because of the discomfort, the abdomen was opened and about 9 pounds (4.1 Kg.) of fluid removed. The peritoneum was found studded with large tubercles. The patient was treated with pituitary and epinephrine in oil and later with epinephrine by mouth. This time there was no apparent effect; the patient was removed from the hospital by relatives, and we have no information concerning the outcome.

Case 4.—The patient was admitted to the Research and Educational Hospital, May 20, 1926. He was a colored man, aged 24, with a history of typical tuberculous peritonitis of five months' duration. His weight on admission was 130 pounds (59 Kg.).

Physical examination and roentgen examination revealed a far advanced tuberculosis with involvement of the entire right lung, pleurisy of both the right and the left side and tuberculous peritonitis. The blood pressure was 122 systolic and 88 diastolic. On June 22, a thoracentesis was made and 60 cc. of straw-colored fluid was removed. On June 25, approximately 1,500 cc. of fluid was withdrawn. On December 28, another aspiration of the right chest was made and 500 cc. of fluid withdrawn. On December 31 another 500 cc. was withdrawn.

After a short period of observation, the patient was treated with calcium lactate, atropine and small doses of pituitary, the latter preparation practically inert, however. After the preliminary loss of weight associated with the reduction of fluid in the pleural and abdominal cavities, the weight curve was practically stationary. On November 16, three doses of an active pituitary preparation in oil were given daily intramuscularly (indicated by the heavy arrow in chart 8). The pulse rate increased, the temperature declined and the weight fell sharply. A short course of digitalis was given and later the patient was put on a Sippy diet for two weeks. The patient ultimately died, in February. The autopsy was performed by Dr. J. P. Simonds, to whom we are indebted for the report:

Autopsy.—Externally, the body, that of a male, appeared poorly nourished. A lymph gland low down in the neck was palpable. The axillary lymph glands were enlarged. The inguinal lymph glands were somewhat enlarged. On the medial side of Poupart's ligament was an old scar, 5 by 11 mm. The level of the abdomen was about the same as that of the chest.

The fat in the anterior abdominal wall was 5 mm. thick. The intestines were everywhere matted together by dense fibrous adhesions. There were yellowish-white nodules, from 1 mm. to almost 1 cm. in diameter. On section, they were cheesy.

Chest, Right Side: The air escaped when the chest was open. In the anterior mediastinum, in both the upper and the lower parts, were large lymph glands, cheesy on the cut surface. The largest above the diaphragm was 2 cm. in diameter and 0.5 cm. thick. Left Side: The pleural cavity was obliterated by adhesions similar in density to those in the peritoneal cavity. In the lower posterior portion was a cavity between the lung and the chest wall, and the diaphragm was filled with turbid yellowish fluid, in which were many flakes of fibrin. The parietal and visceral pleurae here were covered with a thick layer of yellowish-white exudate. Elsewhere in the pleura there were easily torn fibrous adhesions. Cheesy nodules were found, the largest 7 mm. in diameter. On the right side, the parietal pleura was much thickened and the inner surface was covered with a yellowish exudate. Between the parietal pleura and the right lung was a cavity filled partly with turbid fluid in which were flakes of fibrin. This cavity was partly filled with air. The parietal and visceral pleurae were adherent over the upper lobe. The lower lobes were collapsed and a yellowish exudate covered them.

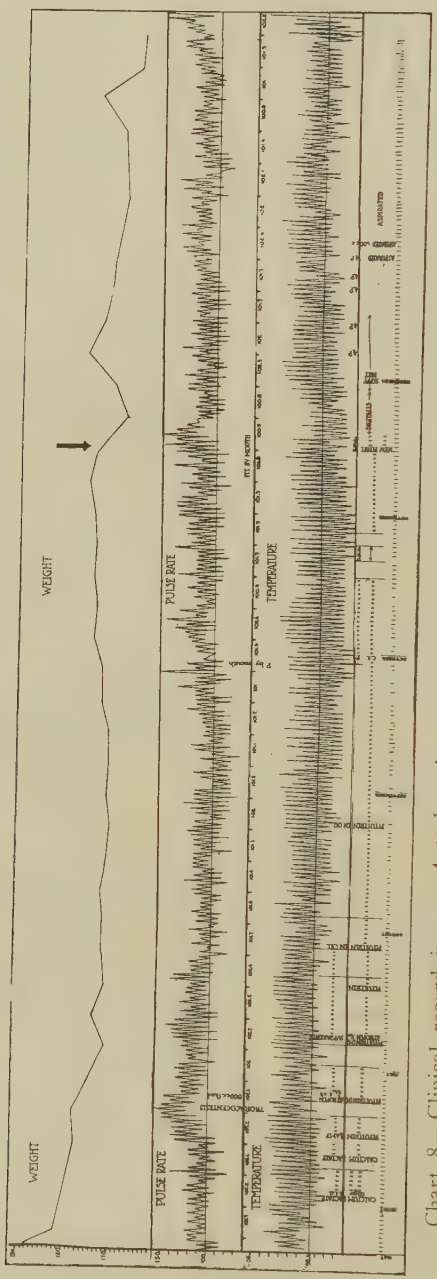

Chart 8.—Clinical record in case 4 (tuberculous peritonitis, bilateral pleurisy and far advanced tuberculosis of right lung). The patient was treated with calcium lactate, atropine and small doses of pituitary.

The pericardium contained blood-tinged, clear fluid (50 cc.) and was shining smooth and glistening.

The heart was the size of the owner's right fist. The foramen ovale was closed. The tricuspid orifice admitted five gloved fingertips; the mitral, three. The heart valves were smooth and thin. The myocardium was pale grayish-red and friable; the aorta was smooth throughout.

The left lung, unopened, weighed 630 Gm. It floated in water with the lower lobe downward. The upper lobe crepitated feebly throughout. The lower lobe, upper quarter, crepitated. The remainder was noncrepitant and had the consistency and feel of spleen. The pleural surface was covered with a thick, yellow-white, fibrinous exudate. The cut surface of the upper lobe was grayish red. Frothy fluid escaped on pressure. The cut surface of the lower lobe was also grayish red. Some frothy fluid was squeezed from the upper part. Pieces cut from that portion and from the deeper parts of the remainder of the lobe floated in water.

The right lung crepitated feebly in the lower and upper part of the upper lobe. The remainder of the lung was completely collapsed and airless. The upper part of the upper lobe was adherent to the chest wall. The interlobar fissure was obliterated. The cut surface was grayish and moderately moist (upper lobe). At the hilum were numerous anthracotic lymph glands with large caseous areas. Pieces cut from the upper part of the upper lobe floated. Pieces cut from the lower lobe sank.

The spleen was markedly enlarged and firmly adherent to the diaphragm and also adherent to all other adjacent organs. It weighed from 6 to 90 Gm. There was an accessory spleen about 2 cm. in diameter, in which were several millimeter-sized, cheesy nodules. The cut surface was studded with innumerable yellowish-white, cheesy masses, from 1 mm. to 1 cm. in diameter. There were sharply circumscribed. The cut surface was dry and cheesy. Some of the masses were round; others were lobulated and irregularly confluent.

The liver was large, the capsule everywhere thickened. In places, it was adherent to adjacent organs. It was firmly adherent to the diaphragm. A large part of the capsule was roughly stripped off with removal of the right lung. On the cut surface, some cheesy masses, from 1 to 15 mm. in diameter, were found. Scattered throughout were numerous cavities. The largest was about 2 cm. in diameter. They contained a thick, yellowish-green fluid, and their walls were from 1 to 2 mm. thick. These were yellowish gray. The liver substance was soft and friable. The lobular markings were indistinct. The process had followed the bile duct.

The pancreas showed postmortem changes. The adjacent lymph glands were markedly caseous. The pancreas itself was not involved.

The right suprarenal gland was markedly enlarged. It was almost transformed into a yellowish, cheesy mass. No suprarenal tissue could be made out with certainty. There might have been a small narrow zone of suprarenal tissue of the extremities. The left suprarenal gland was also replaced by a yellowish, cheesy mass.

The stomach was free from ulcerations. The peritoneal surface was studded with cheesy masses.

The right kidney was larger than normal. The capsule stripped easily leaving a smooth surface. There was fetal lobulation. The cortex showed numerous red areas the size of a pin point. The cortex measured from 5 to 7 mm. in thickness. The markings were indistinct. Two separate and distinct pelvises were revealed each opening into its own ureter; the ureters united before entering

the bladder. In one papilla was a millimeter-sized cheesy mass. A larger cheesy mass 6 by 8 mm. was seen in another, and in three papillae the cheesy masses, 2 by 5 mm., were observed. The left kidney was somewhat larger than normal. The capsule stripped easily. The surface was the same as in the right kidney. The cortex was from 5 to 8 mm. thick. The cortical margins were not normally distinct. The bladder showed nothing abnormal.

Anatomic Diagnosis.—Generalized tuberculous peritonitis; tuberculosis of the abdominal, retroperitoneal and mediastinal lymph glands; disseminated tuberculosis of the spleen; tuberculosis of the accessory spleen; tuberculous cholangeitis; pyopneumothorax; chronic tuberculous pleurisy, bilateral; compression atelectasis of the lower lobes of both lungs; tuberculosis of the right kidney; double pelvis and urethra of the right kidney; disseminating tuberculosis of the liver; cloudy swelling of the liver and the kidneys; fetal lobulations of the kidney, and tuberculosis of both suprarenal glands.

Histologic Observations.—Right Lung: The pleura was covered with a thick layer that in the outer portion was fibrinous and in the deeper parts caseous. The endothelium covering the pleura was completely lost. There was an attempt at organization of the necrotic material resting on the pleura. The pleura itself was thickened, edematous and diffusely infiltrated with lymphocytes, large mononuclears and occasional plasma cells. The blood vessels were widely dilated and had thin walls. The lung tissue in this section showed the alveoli collapsed. There was much pigmentation with coal dust. The bronchi showed considerable desquamation of the epithelium and many contained a finely granular or fibrillar material, in which were scattered polymorphonuclear leukocytes. In the collapsed lung tissue were a number of miliary tubercles.

Liver: Near the center of the section of the liver was a cavity in which was coagulated granular material, some of which was yellow. The inner part of the wall of this cavity was necrotic and caseous. Surrounding this was a narrow zone of fibrosis in which was an occasional tubercle. Elsewhere the liver showed marked postmortem changes. Many of the liver cells still showed considerable fat. Scattered irregularly through the section was a moderate number of miliary tubercles.

Kidney: The section of the kidney showed a large caseous area separated from the remaining kidney substance by a narrow zone of fibroblasts and lymphocytes with an occasional giant cell. Elsewhere there was marked postmortem change in the tubular epithelium and a fairly uniform, moderate increase of connective tissue between the tubules. Many of the tubules in the cortex contained casts. The glomeruli, in general, were richer in cells than normal. In some, the individual capillary loops had lost their identity and the glomerulus appeared as a rather dense cellular mass. None of them showed amyloid. A few glomeruli had been completely transformed in the dense hyaline tissue.

Suprarenal Gland: In this section there was only a small amount of recognizable suprarenal tissue. The remainder was composed of a large caseos mass surrounded by a zone of fibroblasts and lymphocytes with here and there a typical tubercle.

The clinical course is interesting only in that it demonstrates that these large doses of pituitrin were able definitely to depress the temperature curve for approximately one week. The administration was followed by an immediate increase in the pulse rate and consequently we dealt with an added strain on a cardiac musculature already depressed.

The clinical application might therefore seem dubious, but the result seems to offer proof of the theory that the diminished permeability is followed by improvement so far as the temperature is concerned. The loss of weight in this case was undoubtedly due to the transient loss of water.

That pituitary given over a long period need not be harmful in suitable cases seems probable from case 5.

Case 5.—A colored man, with far advanced pulmonary tuberculosis (large cavity in the left upper lobe), had been transferred from the Cook County Hospital. He had been under observation there from April 10, 1926, to November, 1926. During this time, his weight had declined from 123 to 110 pounds. After being under observation two weeks at the Research and Educational Hospital, he was given three successive doses of pituitary (5 units per dose, in oil, intramuscularly). The temperature diminished, but the pulse increased considerably and there was a loss of weight similar to that observed in patient 4. Later, pituitary was given once a week for five months. During this time, the weight gradually increased and the sputum diminished. For a period of three weeks, large capsules of hydrous wool fat were given. A year after admission, the weight was 140 pounds (63.5 Kg.), and the clinical condition was stationary (chart 9). In view of the fact that the patient had a large left apical cavity, the desirability of collapse was considered and the patient was transferred to the surgical service. He survived the immediate effects of the operation, but died suddenly two days later.

Autopsy.—The body was that of a colored man, aged 35; it was 62 inches in length and weighed 144 pounds (65.3 Kg.).

The left lung had adhesions about the upper portion, and smaller adhesions about the other portions. A large irregular cavity, 9.5 by 7.5 cm. was found in the left upper lobe. The cavity was filled with thin, reddish pus. The wall of the cavity was from 0.5 to 1 mm. thick. It was grayish white, covered on the inside with flat, yellowish-white plaques. In the middle of the posterior wall was a nodule, 3 mm. in diameter, which contained a cavity communicating with the branch of the pulmonary artery. In the right upper lobe were strands of anthracotic scar tissue surrounding firm, cheesy and calcified nodules, 4 mm. in diameter. Single small nodules and areas of granular consolidation were present in the left lobe.

The heart weighed 320 Gm. The left ventricle had a diameter of 13 mm., the right ventricle one of 7 mm. The aorta measured 60 by 42 by 36 mm. Small plaques were observed in the left coronary artery, and larger ones in the arteria abdominalis.

The intestines showed irregular ulcerations extending down to the muscularis and with slightly thickened undermined edges in the cecum and lower parts of the colon ascendens. There were adhesions about the appendix, which was dilated and contained near its origin a whitish nodule, 5 mm. in diameter.

The liver weighed 1,440 Gm., and showed distinct markings. The pancreas weighed 100 Gm.; the spleen, 120 Gm. The left suprarenal gland presented a light yellow cortex. The right kidney weighed 160 Gm., the left, 150 Gm. The capsule was adherent. The surface was studded with small irregular, grayish-brown nodules. A gray nodule the size of a pinhead was present in the medulla of the left kidney. The brain weighed 1,370 Gm. Besides these changes, a recent thoracoplastic operative wound was observed, with resections of half of the first left rib.

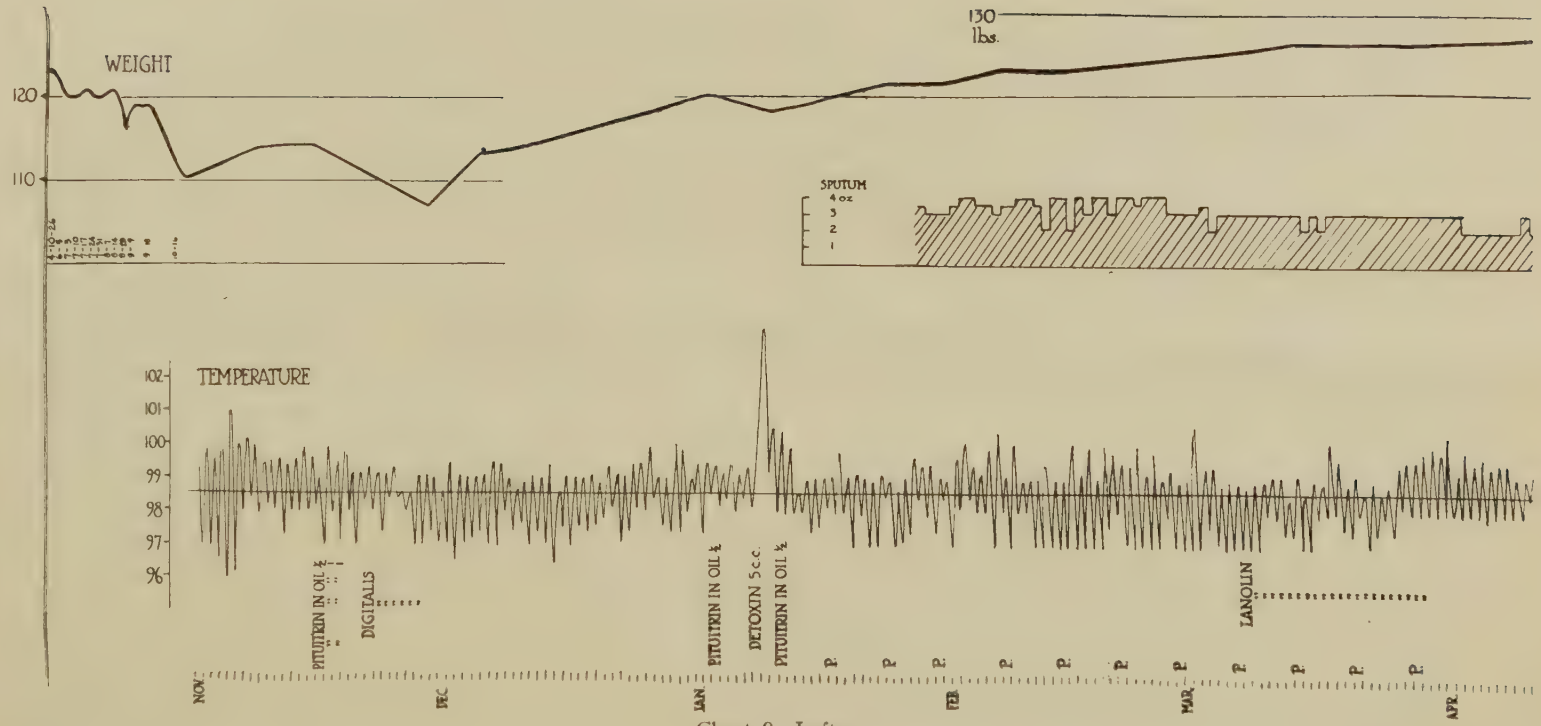

Chart 9—Left

Chart 9.—Clinical record in case 5 (far advanced pulmonary tuberculosis). The patient was treated with pituitary.

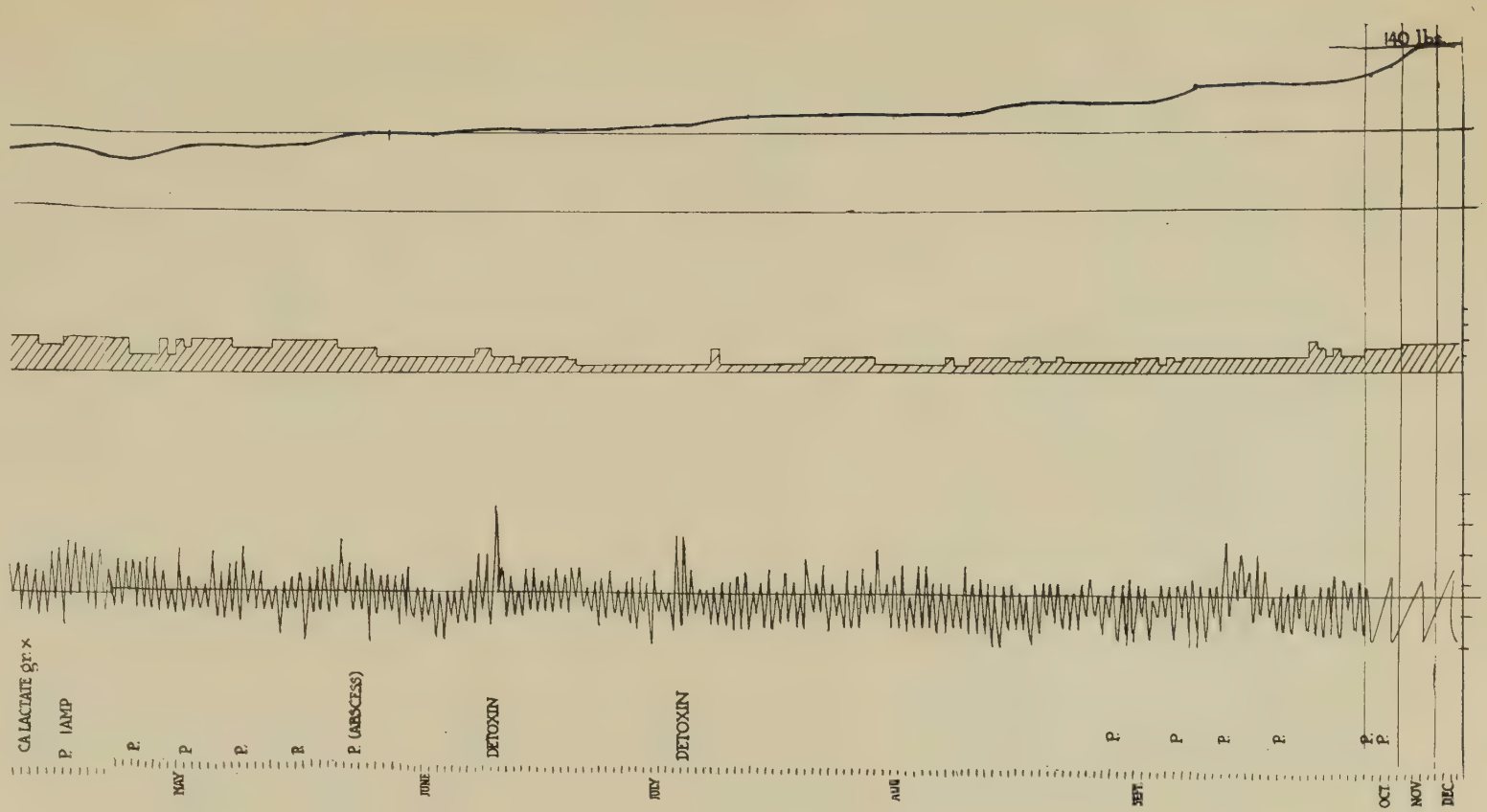

Chart 9—Right

Anatomic Diagnosis.—Ulcerative tuberculosis of the left upper lobe of the lung; chronic fibrous tuberculosis of the right upper lobe; bronchitis and bronchial pneumonia of the left lower lobe; fatty degeneration of the liver; cloudy swelling of the kidneys; ulcerative typhlitis; edema of the brain; recent thoracoplasty.

Histologic Observations.—Lung: The wall of the cavity in the left upper lobe consisted of cellular granulation tissue with dilated capillaries. Toward the lumen the granulation tissue gradually passed over into cheesy masses. In the granulation tissue were many typical Langhans giant cells and a few young tubercles. Groups of foreign body giant cells contained peculiar calcified round bodies. In the outer portion, the wall was composed of fibrillar connective tissue with glandlike structure. Some of the arteries showed a marked thickening of the intima. In the left upper lobe, single tubercles were observed, composed of a cheesy center surrounded by dense scar tissue, with much anthracotic pigment. In the surrounding parts a few giant cells were assembled but there were no young tubercles. The lung tissue adjacent to the tubercles with the fibrous capsule contained many accumulations of lymphocytes.

Lymph Glands: The lymph glands presented a diffusely calcified mass enclosed in a thin capsule of fibrous tissue. Near the capsule was a giant cell containing a calcified body. The other parts of the gland were hyperemic with much pigment.

Liver: The liver cells contained small fat droplets. Near the center of the acini were granules of dark brown pigment besides the fat droplets. There were infiltrations of round cells in the periportal connective tissue.

Kidney: The kidneys showed circumscribed areas of atrophy with hyaline glomeruli and round-cell infiltration. There was swelling of the epithelium of the convoluted tubules in the parts between the atrophic areas. Much fat was present in the lining epithelium of the ascending part of Henle's loops and the collecting tubules.

Spleen: The spleen showed fibrosis of the pulp, and small follicles without centers.

Thyroid Gland: The thyroid gland revealed medium-sized vesicles lined by flat epithelium and filled with homogeneous colloid.

D. A STUDY OF THE REACTION TO EPINEPHRINE IN TUBERCULOUS PATIENTS*

The reaction of tuberculosis patients to the subcutaneous injection of epinephrine has interested a number of observers. Particularly Guth,[1] Glaser,[2] Dugge,[3] and Samogyi[4] have studied the reaction in detail, and have associated the presumptive autonomic status revealed by the reaction, to the clinical course of the disease.

Their studies have revealed the change in the reaction of the body that takes place as the result of the infection, the early cases revealing lability of the autonomic system, late cases showing anergy of either vagus or sympathetic reactions.

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* Reprinted from Am. Rev. Tuberc. **18**:616 (Nov.) 1928.

1. Guth, E.: Beit. z. Klin. d. Tuberk. **53**:94, 1922; **55**:1 and 3, 1923; **60**:39, 1925.
2. Glaser, W.: Ibid. **55**:390, 1923.
3. Dugge, M.: Ibid. **65**:96, 1927.
4. Samogyi, S.: Ibid. **60**:619, 1925.

Samogyi has examined the relation of the autonomic reaction to the injection of specific antigen (tuberculin). He believes that the primary reaction is vagotonic [tending to sleepiness (without refreshment), thirst, water-retention and increased weight, oliguria, globulinaemia, etc.], and later, with maximum absorption of the antigen, a sympatheticotonic stimulation occurs with reversal of the picture.

Our own interpretation of this phenomenon is based on the commonly observed diphasic character of autonomic reactions, and we have assumed that, while the primary reaction is vagotonic in its character, the sympatheticotonic reaction which follows is that which we associate with improvement.

During the course of the past year we have been interested in an examination of the reactions of tuberculous patients, in an endeavor to correlate blood chemistry, the autonomic status, the immune reactions, the skin sensitivity to light, etc., with the clinical-pathologic status existing at the time of examination. Incidental to this study, the patients were injected with 0.5 cm. of 1 to 1000 synthetic suprarenin (Metz), and the systolic and diastolic blood pressures and the pulse rate were measured every 5 minutes for one hour after injection. In addition, observations were made for a second hour following massage of the area of injection, a procedure which makes evident the fact that the epinephrine has not been oxidized or destroyed, but that a further effect can be obtained with expression of further epinephrine from the subcutaneous depot.

In this paper we wish merely to present the epinephrine curves so obtained, and the conclusions that may tentatively be drawn from a survey of the reactions as they are related to the clinical status of the patient.

We have made our classification in two ways: first, on the basis of *minimal, moderately advanced* or *far-advanced* cases and, second, on the basis of the status of the *weight curve* at the time of examination. We have grouped these latter curves as gaining, stationary and losing. We are aware, of course, that this classification cannot take into consideration the possibility that in some cases we are dealing merely with water-retention and with no real improvement of the patient. The weight curves for several months before and after the day of examination are presented in the curves shown on charts 1 to 4.

In chart 5 the individual curves have been arranged on the basis of the systolic blood-pressure reaction. Group 1, for instance, comprises the cases in which there was an immediate increase, with a persistence of this increase during the course of the next hour; group 2, those cases in which there was an immediate increase with a subsequent fall; group 3, those cases in which there was a primary increase of varying extent with

a subsequent return to the normal; group 4, those cases in which the primary reaction was still sympatheticotonic, but in which considerable depression followed during the course of the next hour. Groups 5, 6 and 7 comprise the cases with a primary depression of the systolic blood pressure, followed either by ultimate recovery or increase (groups 5 and 6), or those cases with a primary decrease and a persistent and long-continued fall in blood pressure (group 7). The abbreviations at the left of each chart indicate the clinical classification, and the black bar indicates whether the patient was gaining or losing in weight or was stationary. The analysis of these cases is presented in table 1.

In chart 6 the same material has been arranged on the basis of the so-called cardiac output (that is, pulse pressure $\times$ pulse rate), and the analysis of the material shown in this chart is presented in table 2.

DISCUSSION

In article IV we report on a study of 100 so-called "normal" individuals.[5] Of these "normal" individuals, however, only 20 proved to be perfectly normal (examination of urine, skin capillaries, roentgenographic, physical, history, etc.). In the larger group there were 9 individuals who gave evidence of a distinctly healed pulmonary tuberculosis (roentgen examination) and 9 individuals with an active parenchymal tuberculosis (roentgen examination), the majority of whom were old chronic cases, in one case with a history going back more than 30 years. When we examine this material and compare it with the sanatorium cases, we find that the average epinephrine reaction for the healed parenchymal cases is increased over the normal, somewhat diminished for the active parenchymal cases, and becomes negative for all the sanatorium material. These relations are brought together in table 3.

It will be noted that the pulse rate is somewhat increased for the healed parenchymal, as well as the active parenchymal cases, and that the weight/length ratio diminishes progressively, as might be expected.

When we analyze the results of table 1, it seems permissible to draw the conclusion that cases that are gaining in weight, irrespective of the anatomic status of the tuberculosis, are cases in which the injection of epinephrine is more often followed by a sympatheticotonic type of reaction, whereas fewer cases are in the gaining group if the epinephrine injection is followed by the vagotonic type. On the other hand if we base our analysis, as we do in table 2, on the so-called "cardiac output," in which the relation of the pulse rate is included, then the reaction seems to have much less significance in its relation to the clinical course.

5. Article IV. The Relation of the Reaction to Epinephrine to the Potassium/Calcium Ratio and to Other Ratios, p. 121.

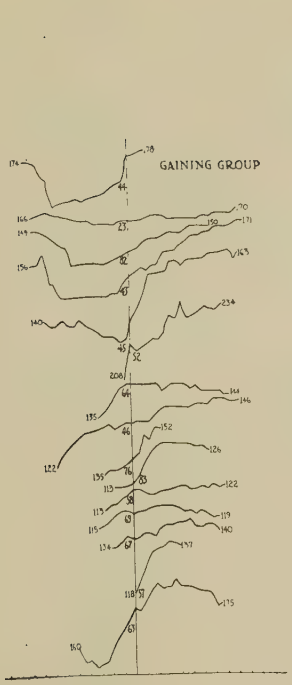

Chart 1

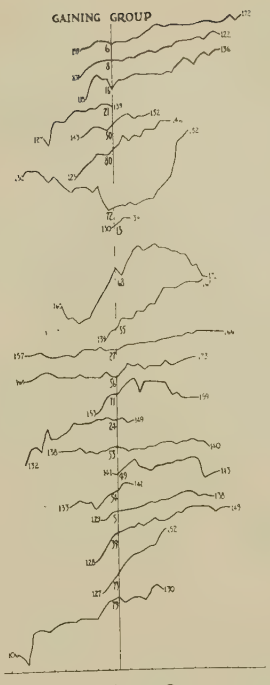

Chart 2

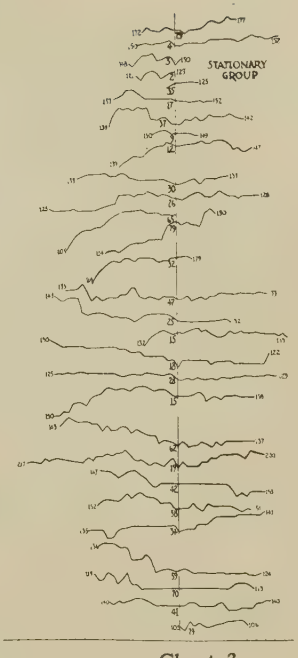

Chart 3

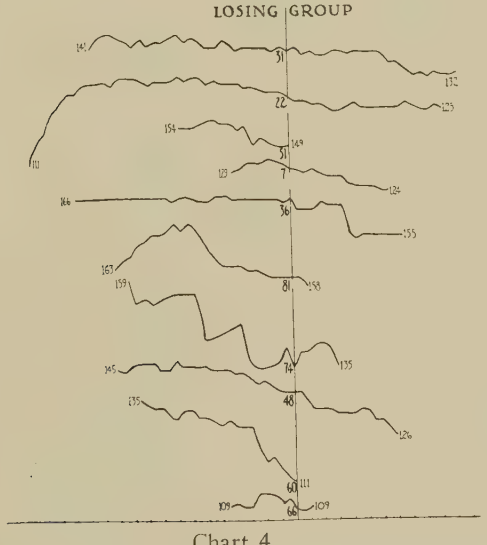

Chart 4

Charts 1, 2, 3 and 4.—Weight-curves of patient used for the study. Center line indicates the day of examination. Abscissae indicate weeks during observation.

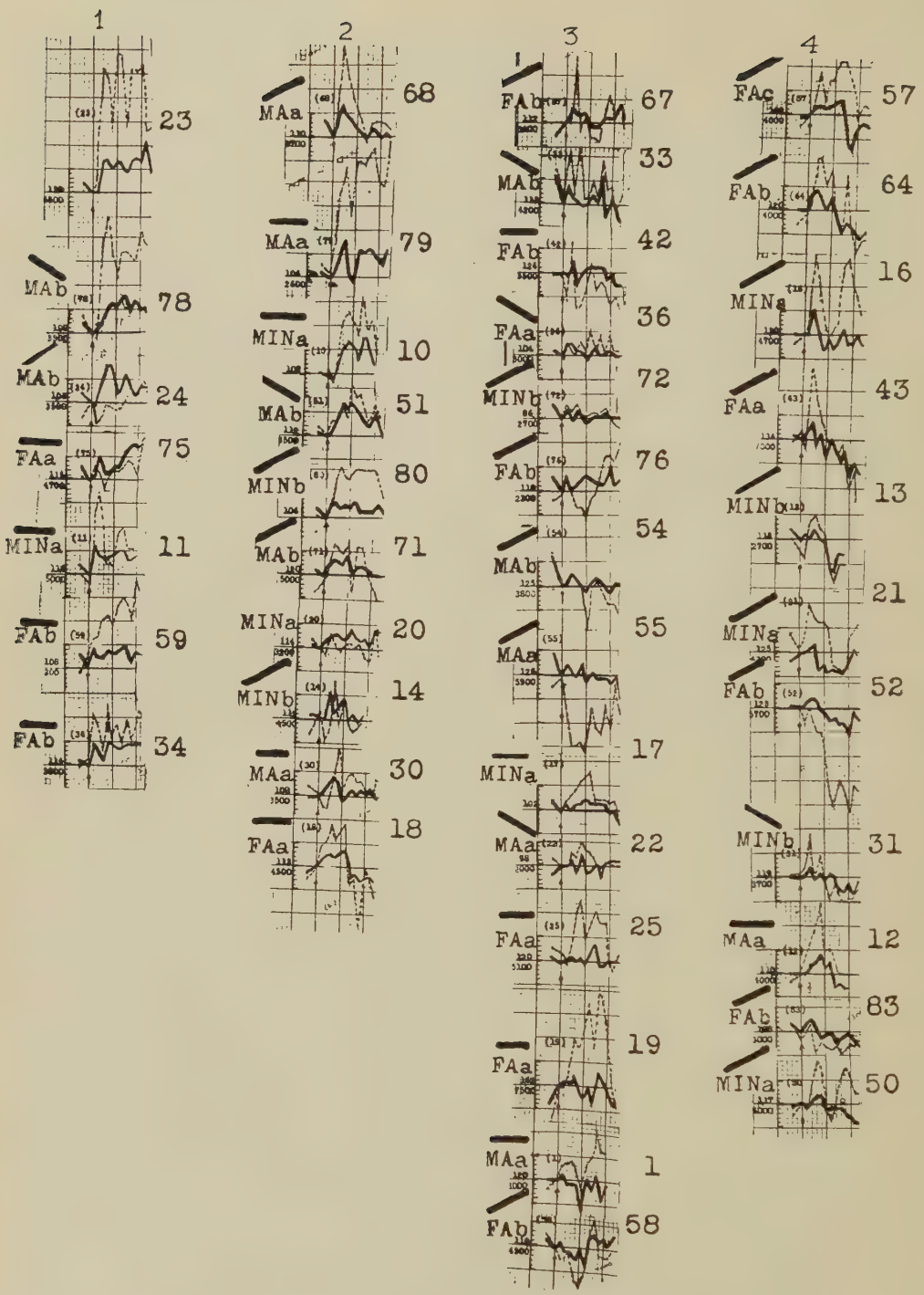

Chart 5.—Individual blood-pressure reactions following subcutaneous injection 0.5 cc. Metz suprarenin 1 to 1000. Classification indicated by abbreviations at left. Weight-cure indicated by direction of black bar. Heavy line of curve indicates systolic blood-pressure. Dotted line indicates so-called cardiac output. Patients indicated at right. Curves classified on the basis of systolic blood pressure.

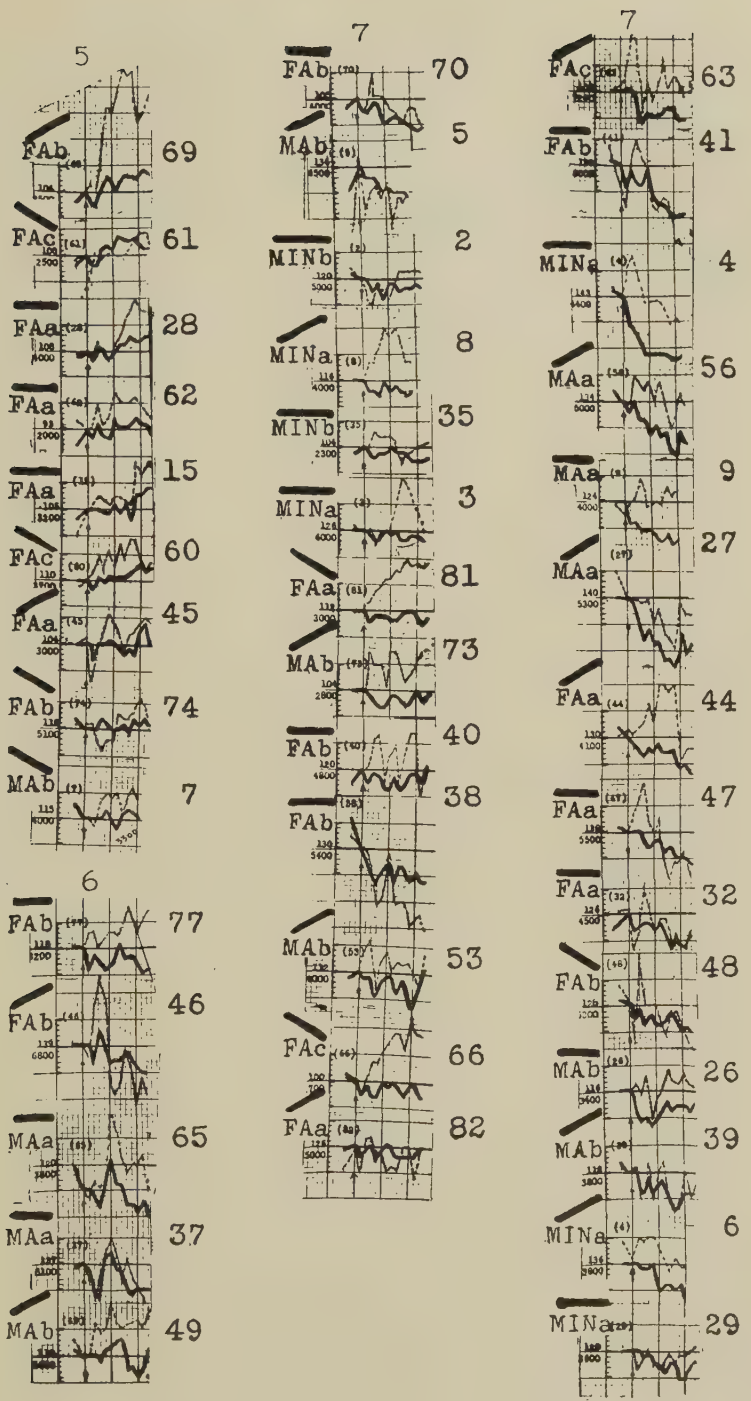

Chart 5.—Concluded

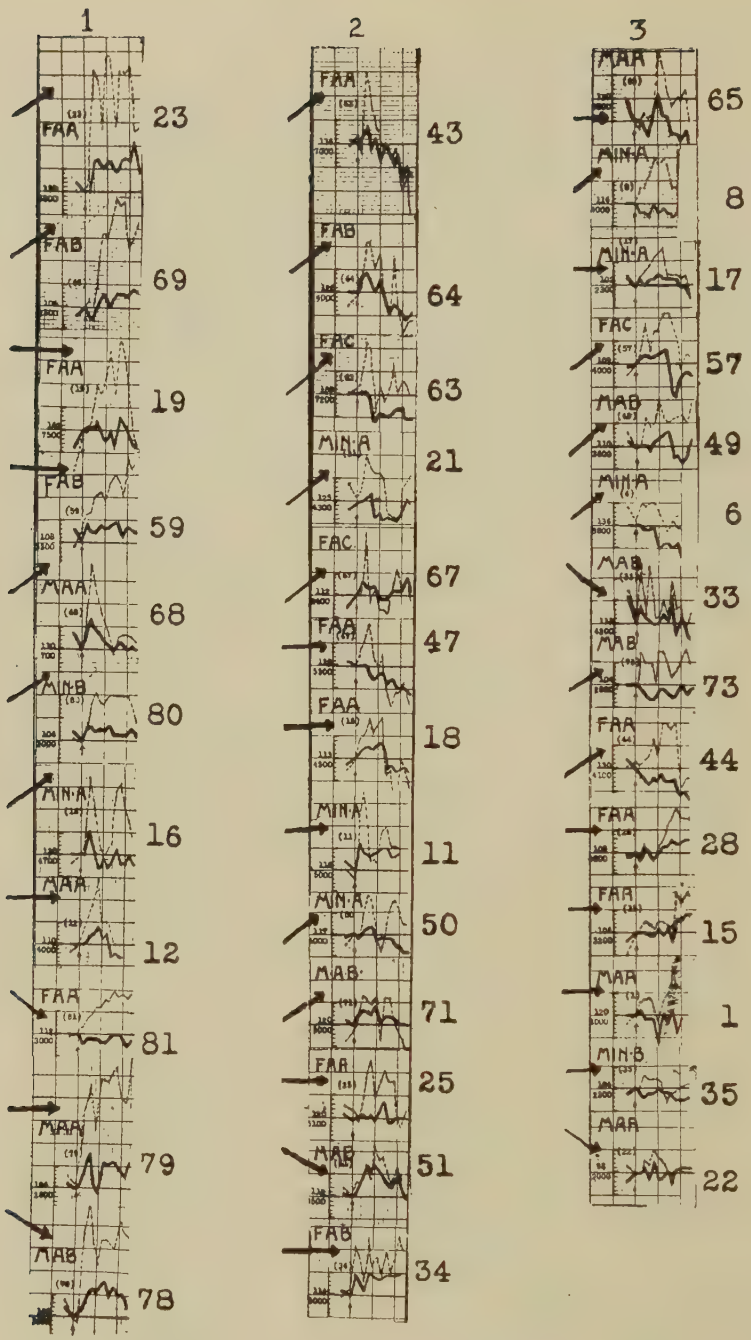

Chart 6.—Individual blood pressure reaction following subcutaneous injection 0.5 cc. Metz suprarenin 1 to 1000. Weight curve indicated by direction of black bar. Heavy line of curve indicates systolic blood pressure. Dotted line indicates so-called cardiac output. Patient's number indicated at right. Curves classified on the basis of so-called cardiac output.

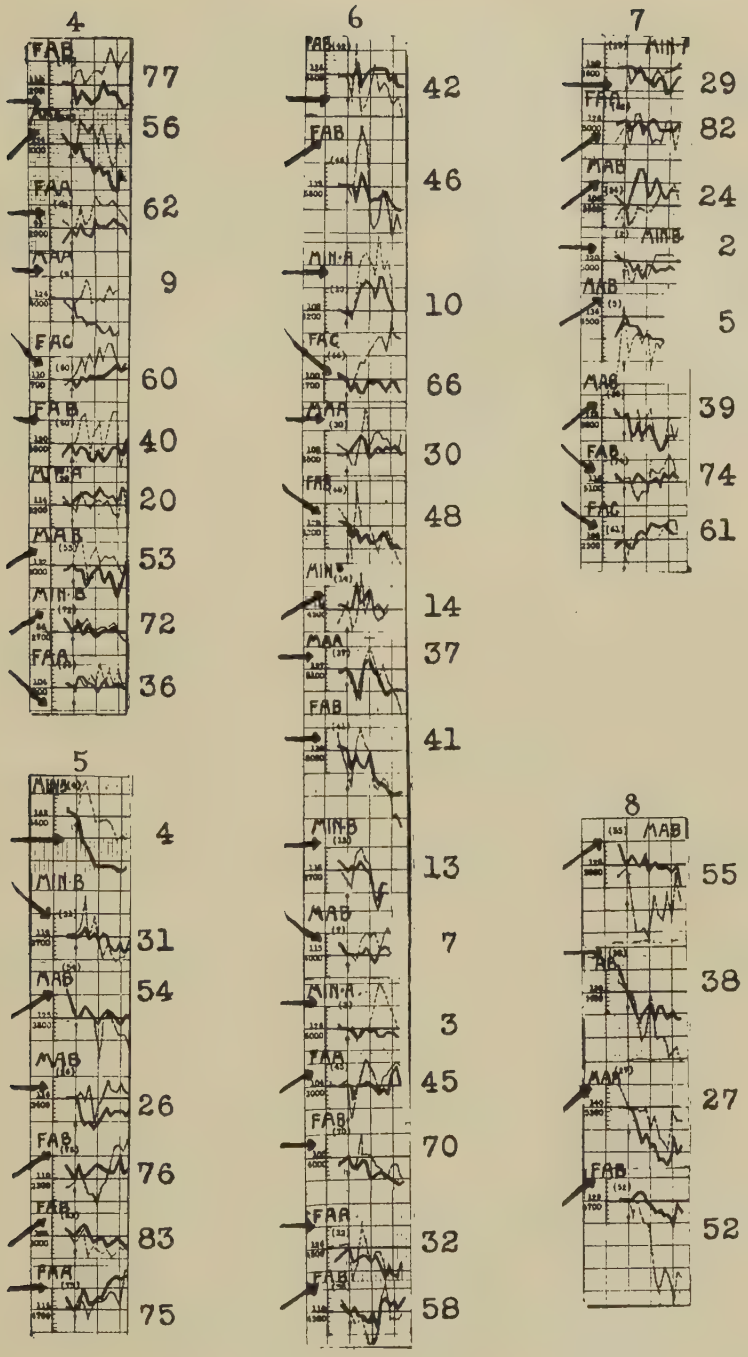

Chart 6.—Concluded

In other words, it would seem that our results tend to confirm a conclusion previously reached,[6] namely, that the sympatheticotonic type of cardiovascular reaction to epinephrine is, in general, to be associated

TABLE 1.—*Groups Arranged on the Basis of Change in Systolic Blood Pressure*

Group (Chart 4)	Number in Group		Gaining, per Cent	Stationary, per Cent	Losing, per Cent	Not Determined, per Cent
		Sympathetic Group				
1	7	Of the 42 cases in the sympatheticotonic				
2	10	group, there are				
3	14	17 far advanced cases (40 per cent),				
4	11	of these	53	40	7	
		13 moderately advanced cases (13 per cent), of these	40	30	30	
		12 minimal cases (29 per cent), of these	58	25	8.5	8.5
		Parasympathetic Group				
5	9	Of the 41 cases in the vagotonic group,				
6	5	there are				
7	27	22 far advanced cases (53 per cent),				
		of these	27	45	27	
		12 moderately advanced cases (29 per cent), of these	50	33	17	
		7 minimal cases (18 per cent), of these	30	70	0	

TABLE 2.—*Groups Arranged on the Basis of Pulse Pressure × Pulse Rate*

	Gaining, per Cent	Stationary, per Cent	Losing, per Cent	Not Determined, per Cent
Sympathetic Group (55 Cases, 66 per Cent) (Groups 1, 2, 3, 4, 5, Chart 6)				
25 far advanced cases (45 per cent) of these	40	48	12	
17 moderately advanced cases (31 per cent) of these	41	35	23	
13 minimal cases (23.5 per cent) of these	54	30	18	8
Parasympathetic Group (28 Cases, 33 per Cent) (Groups 6, 7, 8, Chart 6)				
14 far advanced cases (50 per cent) of these	35	35	30	
8 moderately advanced cases (28 per cent) of these	62	25	12	
6 minimal cases (21 per cent) of these	16.6	83		

TABLE 3

Number of Cases	Type of Cases	Age	Weight / Length*	Pulse	Epinephrine† Reaction, per Cent
	So-called Normal Material				
20	Normal	38	229	66	15
9	Healed parenchymal	42	221	76	21
9	Active (chronic) parenchymal	58.7	215	78	11
	Active Sanatorium Material				
36	Active, gaining	28.6	195	89	—5
32	Active, stationary	32.7	196	88	—4
13	Active, losing	33.2	180	91	—5

* Weight in pounds divided by length in inches.

† The figure represents the average percentage of increase or decrease of pulse pressure for one hour following epinephrine injection as compared with the preinjection level.

with increased resistance to tuberculosis, estimated either on the gain in weight of the patient or on the relative chronicity of the lesion. This becomes apparent too, when we analyze table 3, where it is to be noted

6. Petersen, W. F., and Levinson, S. A.: Am. Rev. Tuberc. **15**:681, 1927.

that the epinephrine reaction is perceptibly increased in the healed parenchymal cases and is still almost normal in the active cases of long standing, while the average for all three sanatorium groups is distinctly vagotonic.

CONCLUSIONS

The analysis of the epinephrine reaction made on eighty-one tuberculous individuals indicates that there is some relation between the type of reaction and the weight curve.

1. A larger proportion of the cases showing a sympatheticotonic type of reaction are in the groups that are gaining in weight.

2. Independently of the anatomical classification, both the healed parenchymal types, as well as individuals showing great chronicity, have, as a rule, a normal or increased sympatheticotonic type of reaction.

E. COMPOSITE CURVES OF CARDIOVASCULAR REACTIONS FOLLOWING INJECTIONS OF EPINEPHRINE IN TUBERCULOUS PATIENTS*

In the preceding article, VIII D,[1] are presented the results of an examination of the epinephrine reaction in tuberculous patients and, on the basis of an analysis of individual reactions, have established correlations between the reaction and the weight curve.

We have taken the same material, and have prepared a series of graphs to illustrate the composite blood pressure curves of these cases: first, when arranged according to the weight curve of the patients, and, second, when arranged according to the clinical classification.

When we compare the results of the systolic blood pressure of the gaining, stationary and losing groups, it is apparent that, while the stationary and losing groups show no increase, the curve of the gaining group has a sympatheticotonic tendency for the first half hour and then shows a drop typical of the normal diaphasic epinephrine reaction (Zondek and Ucko[2]).

On the other hand, the pulse rate, which is practically level for the stationary and gaining groups, increases progressively in the losing group.

The curve of the so-called cardiac output (pulse pressure $\times$ pulse rate) indicates the most marked increase in the gaining group.

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* Article by DeTrana, G. E., and Hillebrand, J. G., reprinted from Am. Rev. Tuberc. **18**:626, 1928.

1. Article VIII D. A Study of the Reaction to Epinephrine in Tuberculous Patients, p. 260.

2. Zondek, H., and Ucko: Klin Wchnschr., 1924, no. 29, p. 1752.

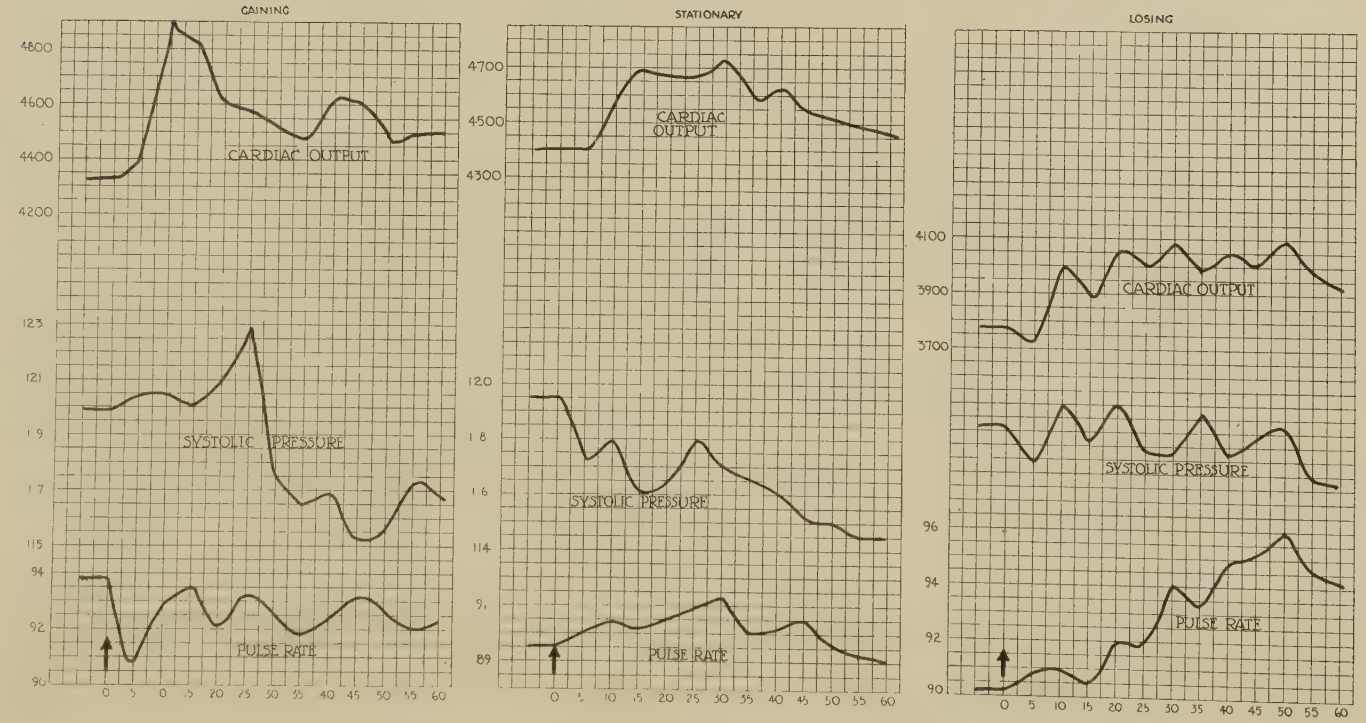

Chart 1.—Composite curves of systolic blood pressure, pulse rate and so-called cardiac output (pulse pressure × pulse rate) of tuberculous patients, classified on the basis of weight curves.

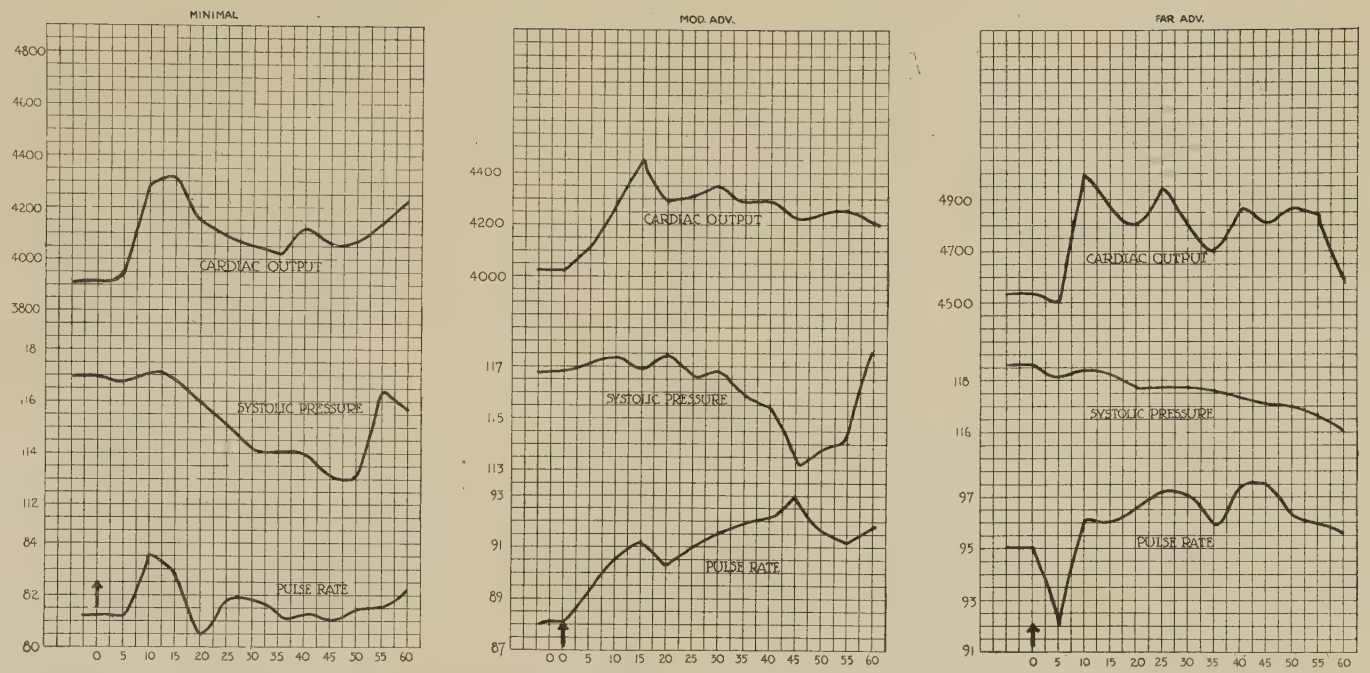

Chart 2.—Composite curves of systolic blood pressure, pulse rate and so-called cardiac output (pulse pressure × pulse rate) of tuberculous patients, classified on the basis of minimal, moderately advanced and far advanced cases.

When we turn to the graphs illustrating the averages for the minimal, moderately advanced and far advanced curves, we note that the average systolic blood pressure diminishes in all three groups (vagotonic), the groups differing only in that the minimal and moderately advanced cases recover within the hour, at which time the far-advanced cases still have a lower systolic blood pressure than before the injection.

The minimal group is much less responsive than the other groups as far as pulse rate is concerned.

CONCLUSIONS

Composite blood pressure curves of tuberculous patients, following the subcutaneous injection of 0.5 cc. of 1-1000 suprarenin indicate that:

1. Minimal, moderately advanced and far advanced cases have in general vagotonic reactions.

2. Recovery from the effect takes place with an hour in the minimal and moderately advanced cases, while the far advanced cases show a prolonged effect.

3. The pulse rate of the minimal cases is affected least, and of the moderately advanced group most. The far advanced cases show a primary slowing of the rate (vagotonic).

4. The curves of the cardiac output are not characteristic.

When arranged on the basis of the weight curves:

1. Cases that are gaining have a primary sympatheticotonic reaction. The systolic blood pressure of the stationary and losing groups remains level or diminishes.

2. The pulse rate of the losing group shows the greatest increase.

F. THE LEUKOCYTIC REACTION OF THE TUBERCULOUS PATIENT FOLLOWING THE INTRACUTANEOUS INJECTION OF AOLAN*

Müller[1] observed that an intracutaneous injection of a bland protein is followed by a transient leukopenia. The reaction is less apparent when the injection is given subcutaneously. The mechanism, according to Müller[2] involves a reorientation of the autonomic apparatus, whereby the splanchnic region undergoes stimulation (parasympathetic) and the peripheral region becomes sympathetically oriented. During this time, when the peripheral arterioles and capillaries are contracted, the leukocytes tend to disappear from the body surface and accumulate in the lungs, liver, and general splanchnic region.

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* Reprinted from Am. Rev. Tuberc. **18**:839 (Dec.) 1928.

1. Müller, E. F.: München. med. Wchnschr. **70**:1163, 1923.

2. Müller, E. F.: The Involuntary Nervous System: An Important Factor in the Body's Resistance, Arch. Int. Med. **35**:796 (June) 1925.

In the preceding articles[3] we have pointed out certain facts dealing with disturbances in the autonomic balance made evident in a study of the blood pressure. In the present paper we wish to present the findings on the same group of patients when the leukocytic curve was followed for one hour after the intracutaneous injection of aolan (a sterile milk preparation). As in the previous paper, the patients were grouped according to the clinical classification of minimal, moderately and far advanced and also on the basis of the weight curve.

Chart 1 illustrates the composite leukocytic curves plotted for the cases as based on the clinical condition.

It will be noted that the average control leukocyte count increases progressively from 8,000 for the minimal to 10,000 for the moderately advanced, and 11,400 for the far advanced cases. The total gain at the end of the hour is greatest for the minimal cases (20, as compared to 10 and 11 per cent for the other two groups).

In studying the curves it should be emphasized that we are dealing with a shifting of the distribution of the leukocytes, that is, from the periphery to the internal organs and *vice versa,* not with a sudden new formation.

In the minimal cases the splanchnic parasympathetic effect is apparently negligible; there is no appreciable peripheral constriction. In the moderately advanced group the automatic instability is obviously much more marked, and we observe a distinct drop in the curve, followed by an increase.

Here evidently the vagotonic reaction of the splanchnic region is much more marked, and with it the contraction of peripheral vessels and peripheral leukopenia become more apparent.

When we turn to the far advanced cases, we have a group which in general is chronic in type. Many of these patients in the hospital were gaining weight or were stationary. Of the total number of far advanced cases (39) only 20 per cent were losing weight. Consequently these represent, to a certain degree, selected resistant material. The vagotonic drop is no longer apparent as it is in the moderately advanced group.

When we turn to the classification based on the weight curve, we find a totally different picture. We are now dealing with mixed groups of minimal, moderately advanced and far advanced cases in each series. As a result, the initial leukocyte level is practically identical, being 10,073, 10,250 and 10,715. When we study the curves, however, we find that both for the gaining and the stationary groups the initial reaction is not indicative of a marked vagotonic effect, but as soon as we turn to the losing group we find a sharp drop in the curve.

3. Articles VIII D, p. 260; and VIII E, p. 269.

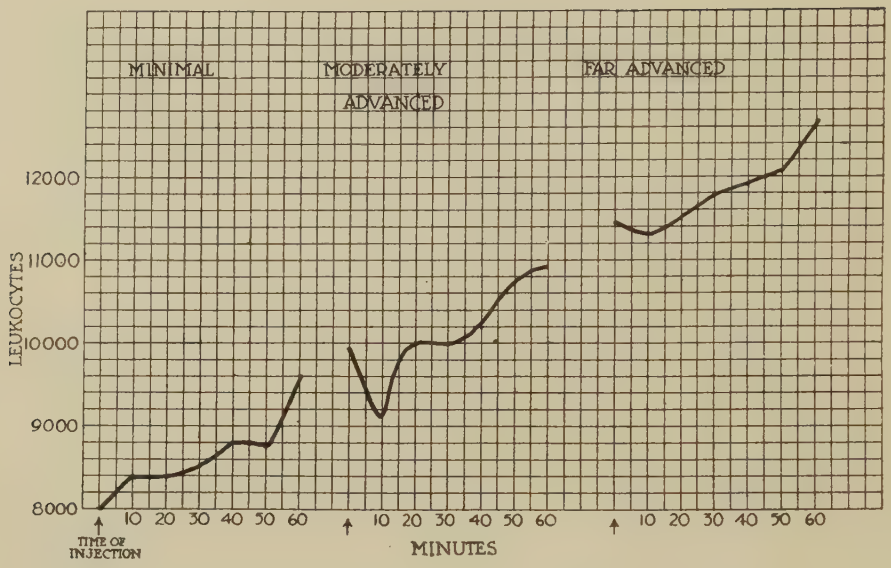

Chart 1.—Composite leukocytic curves following intracutaneous injection of aolan classified on clinical status.

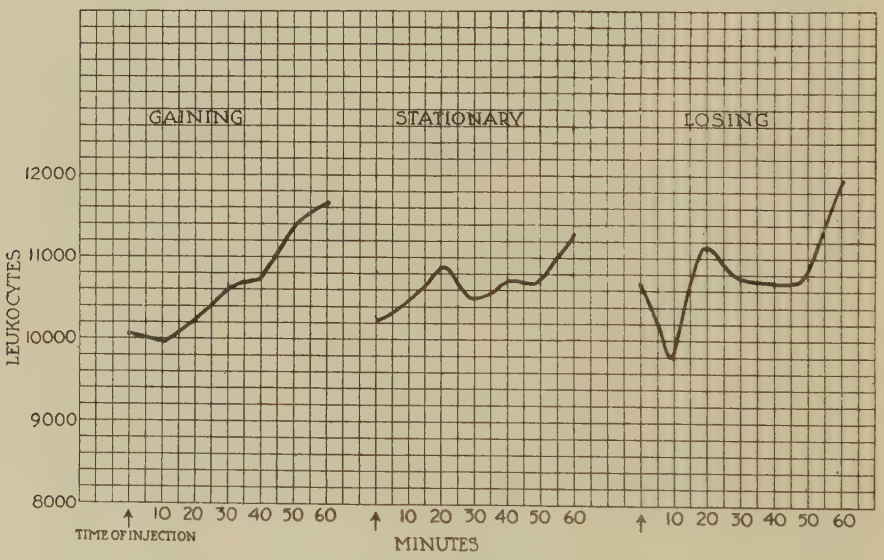

Chart 2.—Composite leukocytic curves following intracutaneous injection of aolan classified on the weight curve.

DISCUSSION

When proteins are injected into a normal individual, a transient redistribution of the circulating leukocytes is effected. Apparently a splanchnic stimulation (splanchnic parasympathetic effect) takes place and leukocytes accumulate in the liver, spleen, lungs, etc. During this time a peripheral leukopenia obtains. When the splanchnic response is very great, the peripheral leukopenia is marked, as we have previously demonstrated.[4] The degree of shifting of the leukocytes gives us, therefore, some measure of the relative stability of the autonomic balance. With great stability no marked fluctuations are to be expected. The reaction is of course akin to the Widal haemoclastic crisis.

These groups of composite curves for tuberculous individuals would seem to indicate that, when classified on the basis of the clinical stage, the minimal group is relatively stable, the moderately advanced group less so (with a splanchnic parasympathetic increase), while the far advanced cases again appear to be more stabile (chronicity, with adequate suprarenal function and general sympathetic status).

The leukocyte curves, made on the basis of the weight-curve classification of these same patients, suggest that the patients that are gaining or are stationary have a minimal parasympathetic response, while the group that is losing shows an exaggeration in this direction.

Differential counts, made before the injection, and thirty minutes and one hour after the injection, show practically no change in the proportion of polymorphonuclear leukocytes to lymphocytes, confirming the assumption that we are dealing largely with a shift in distribution between the periphery and the splanchnic region.

CONCLUSIONS

A study of the leukocyte curves of tuberculous patients, following an intracutaneous injection of aolan, indicates that for the minimal, moderately and far advanced cases, an increased splanchnic parasympathetic effect is associated with the moderately advanced group. When examined on the basis of the weight-curve grouping, the losing group appears to be the only one showing marked splanchnic parasympathetic effect.

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4. Petersen, W. F., Milles, G., and Müller, E. F.: Ztschr. f. d. ges. Exp. Med. **60**:336, 1928.

IX. THE INTRACUTANEOUS REACTIONS TO INJECTION OF PHARMACOLOGIC SUBSTANCES DURING CHILL AND FEVER

In order to determine in some measure the extreme effects of vascular changes on the picture obtained when the intracutaneous pharmacologic tests are made, we examined the reaction in patients during the course of malarial innoculation, the determination being made before inoculation, during the time of chill and during the period of perspiration.

In the chart, we have illustrated the relative sizes of the wheals and the flares at the sites of injection of epinephrine, morphine, thyroxin and caffeine.

The wheal at the site of the injection of epinephrine during the time of the chill was somewhat reduced (on an average, from 10 to 15 per cent), while the flare was much more reduced. This was particularly apparent in patient 2. During sweating, the wheal regained its original size, and in two patients, the flare became much larger than under normal conditions.

With morphine, too, during chilling, there was an apparent reduction of both the wheal and the flare, except in patient 4.

With thyroxin, the wheal was increased during the time of the chill in two patients, but no flare appeared. With caffeine, there was an increase in the size of the wheal during chilling in patient 1, but a reduction in patient 3, so that the results were inconclusive.

During chilling, the autonomic orientation is such [1] that the skin is distinctly sympathetic, while the visceral area is parasympathetic (these terms being used here to designate the state of the capillary bed). During chilling, too, epinephrine is being thrown into the circulation in increased amounts and apparently it accentuates the constriction manifest in the peripheral vessels.

A reduction in the size of the wheals and flares at the sites of injection of epinephrine and morphine made evident during chilling might, therefore, justify us if we interpret reduced size of wheals and flares in general as indicative of an increased sympathetic peripheral tonus.

On the other hand, the wheals at the sites of injection of thyroxin and of caffeine appeared somewhat increased during chilling in two patients, giving further evidence that the effects of thyroxin and caffeine are in direct contrast with the effect of epinephrine.

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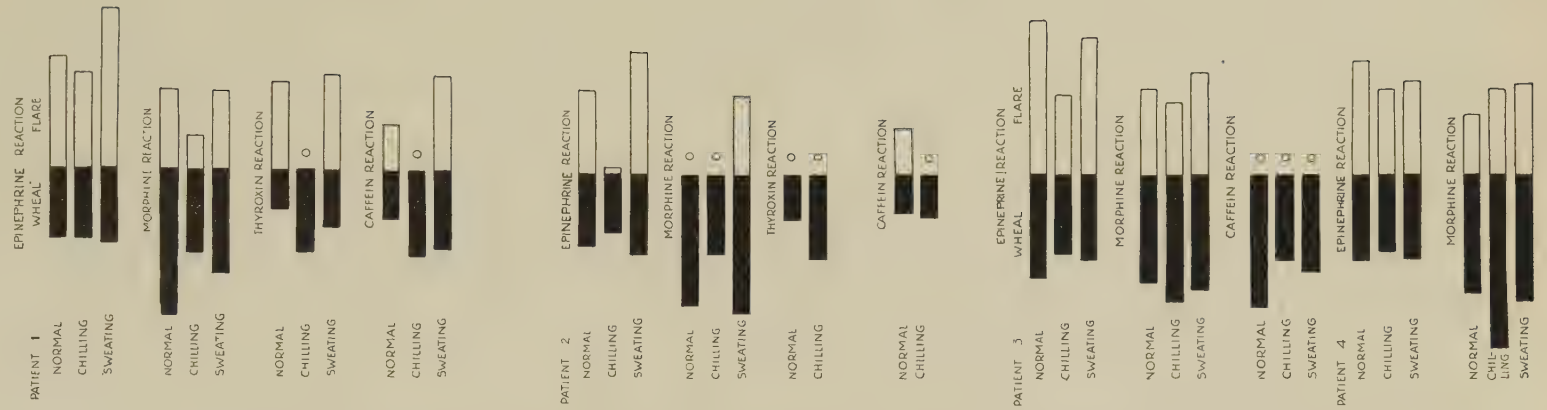
1. Petersen, W. F., and Müller, E. F.: The Splanchnoperipheral Balance During Chill and Fever, Arch. Int. Med. **40**:575, 1927.



A comparison of the sizes of the wheals and the flares at the sites of injection of the pharmacologic substances during malarial inoculation with their sizes under normal conditions.

X. DISCUSSION AND DEDUCTION

CONTENTS

General Considerations
- Study of the Individual Constitution
- Views of Kraus, Bauer, Verschuer and Others

The Slender (Asthenic) Versus the Heavy (Pyknic) Person
- The Sympatheticotonic Versus the Vagotonic Type
- The Thyroid Type

Autonomic Equilibrium
- Daniélopolu's Concept of Vegetative Tonus
- Autonomic Equilibration and Increasing Amplitude of Response
- Schilf's View of Autonomic Antagonists

The Chemical Equilibrium
- Rôle of Calcium and Potassium and the H-Ion Concentration
- Confusion of the Terminology Involved
- Clinical Grouping of Vagotonic and Sympatheticotonic Persons
- Rôle of Cholesterol

The Skin
- Its Autonomic Importance
- Local Resistance
- Herpes and the Splanchnoperipheral Balance
- Respiratory Tract
- Gastro-Intestinal Tract and Change of Temperature

Exophthalmic Goiter

The Nervous Patient

Glaucoma

Tuberculosis
- Constitution
- The Autonomic Status
- The Vascular Reaction to Tuberculin
- Correlations Based on Clinical Classifications, Weight Curve, Clinical Prognosis and Fatalities
- Calcium
- Cholesterol
- Reactivity of the Skin
- Leukocytic Reaction
- Therapeutic Considerations

GENERAL CONSIDERATIONS

In the preceding group of papers, an effort has been made to correlate a number of measurable biologic reactions observed in normal persons and in patients, with each other, with clinical symptoms and with resistance to an infectious disease, i.e., tuberculosis.

In making the tests, we have sought to employ such as might presumably give information concerning the vegetative status of the individual, more particularly the status of the vascular system and the

epidermis. We have sought, furthermore, to determine whether such a vegetative or autonomic status is related to the genotype or whether it is conditional (paratype, and therefore modified by preexisting and latent infection).

Incidentally, we have sought to determine what alterations in the tests that we have employed are indicative of increased or decreased resistance to tuberculosis and what therapeutic deductions might be drawn from such indications.

In view of these particular interests, we cannot avoid a preliminary discussion of certain concepts concerning the vegetative status of the organism and the relation to the constitution in its widest sense.

Study of the Individual Constitution.—It is perhaps a natural swing of the cycle that is bringing medical interest back to an analysis of constitution and conditional reactivity. The triumph of the "era of specific etiology" had completely overwhelmed every thought of constitutional differences in reactivity. Obvious clinical experience was discredited and discarded when in conflict with experimental results from the animal laboratory. Correction has followed, however, because of the obvious fallacy of the underlying method. Precise clinical observation and animal experimentation brought incontrovertible evidence that neither in man nor in animals do like reactions necessarily follow like insults. Even the physiologists and the pharmacologists have recognized that normal animals in deep anesthesia offer a test object totally different from sick patients.

Recognition of the importance of differences in the host has come from the epidemiologist, as well. Thus there are differences in reactivity of the skin and the mucous membranes, respiratory, as well as gastro-intestinal, which determine in a large measure one's liability to infection, as Arnold [1] has recently pointed out.

The scientific study of the individual constitution has been under way from two important nonmedical sides. The earlier anthropologist sought to formulate and define racial groups. More recent studies have been broader and have sought to establish general types irrespective of racial grouping. To this comes an added impulse through the modern study of heredity.

Naturally, physicians have sought to make use of these two lines of approach and have applied them particularly to noninfectious diseases—in which "heredity" and "constitution" have never quite been denied. But emphasis on anthropologic and genetic phases savors too much of predetermination to be wholly acceptable to the medical observer. The conditional factors of environment, of tissue experience,

1. Arnold, Lloyd: J. Hyg. **29**:82, 1929.

of preceding infection, of food, of light, of autonomic training (particularly of the skin), of climate—these must be of equal importance in variable susceptibility to infection, and resistance to one already established. However, many fruitful clinical observations and correlations have taken origin from these two sources. The literature is too large to be discussed, but a recent paper of Draper [2] and his co-workers is illustrative.

Views of Kraus, Bauer, Verschuer, and Others.—"Constitution" as a factor in the disposition to disease means different things to different investigators, depending on their particular interests.

We may, for instance, with Leo Loeb regard constitution as a synthesis and vital unification—the "individuality differential"—a view held by Martins and his school, as well; or go to the opposite extreme with Draper and examine everything from a purely anthropometric point of view. Bauer,[3] on the other hand, discounted the value of the various anthropometric "indices" of this school, but nevertheless limited the term to the "genotype." Pfaundler stressed the importance of environmental (conditional) forces, i. e., the "paratype."

Many physicians have sought to group persons according to the presumptive reactivity of their glands of internal secretion and speak of the "hypophyseal," the "thyroid," or the "adrenal," type. Stern worked out a rather elaborate "glandular formula" and Pende [4] theorized considerably in this direction. Of course, such a classification is attractive because it makes more easy the correlation of genotype and phenotype, the endocrine glands acting, presumably, in the modification of the inherited structure. With definite evidence of nervous control of the suprarenal (Cannon) and thyroid glands (Ascher [5]), the circles of biologic control become ever more intricate.

Kraus [6] and his school, primarily clinical in orientation, stressed the idea of "personality," the term "Syzygiologie" having been coined for the new field.

The novelty of this point of view lies in the fact that it emphasizes the periphery of the organism, the region in which the metabolic processes are going on, and particularly the exchange between the cell and its environment, i. e., the membrane of the cell. As components of this system are to be regarded all factors that play into this intricate

2. Draper, G.; Allen, Grace, and Spock, Jane: Studies in Human Constitution, Clinical Genetics, J. A. M. A. **92**:2149 (June 29) 1929.

3. Bauer, J.: Klin. Wchnschr. **8**:145, 1929; Ann. Int. Med. **2**:127, 1928.

4. Pende, Nicola: Constitutional Inadequacies, Philadelphia, Lea & Febiger, 1928.

5. Asher, L., and Pfluger, O.: Klin. Wchnschr. **6**:1614, 1927.

6. Kraus, F.: Allgemeine und spezielle Pathologie der Person, Leipzig, Georg Thieme, 1926, pt. 1.

exchange, either accelerating or inhibiting it, as for instance, water, the colloid electrolytes, salts, combinations of cations, the buffer system, hormones, definite endogenous and exogenous irritants and poisons, as well as the catalysts.

The local and transient balance of this intricate mechanism is not determined only by the degree, the direction and the rapidity of the specific cell functions, but also by the degree and directions of the vegetative nervous irritability. The vegetative nervous system has the function of regulation—regulation in the sense that it determines to a large degree the distribution of the electrolyte reserves from one place to another.

In the logical development of this idea, Kraus came to the conception of a phylogenetically long established "Tiefen-person," that individualism of the most vital and most profound sort, a vital component of the constitutionally and primarily ordained protoplasm. This fundamental individualism is to be placed in contrast with the centrally organized and much younger cortical personality.

One of the great advances which lies in this concept of the constitution is, we believe, the fact that it emphasizes the impossibility of trying to coordinate isolated observations on both nervous systems (vegetative and central) without a proper regard for all the other factors of the vegetative apparatus. On the other hand, it is of use in the proper evaluation of the vegetative nervous system for all of our clinical problems. We shall refer repeatedly to the general idea.

Daniélopolu [7] also stressed the importance of the periphery, i. e., the terminal organ as the site at which the basic orientation of the individual is determined.

Perhaps, the simplest and most useful of medical points of view of constitution is that of von Verschuer,[8] who defined it merely as "the relative (constitutional) status in the terms of resistance," stressing, nevertheless, that constitution (= Körperverfassung of Tandler = status,) is an organically fixed condition.

Bauer emphasized the importance of constitution in differentiating a group of biologically inferior persons—extreme variants from the normal—in adaptability, in vitality and in resistance. This, too, might seem a most useful concept for the physician.

He was content for practical purposes to group persons as:

Slender	Normal	Heavy
(Dolicho, or asthenic type with small heart)	(Normotype)	(Brachy, or pyknic type)

7. Daniélopolu, D.: Presse méd. **31**:649, 1923.

8. Von Verschuer, O.: Klin. Wchnschr. **8**:769, 1928.

The French have always associated the first group with lessened resistance to pulmonary infections; the latter group with gout, rheumatism, diabetes and arteriosclerosis.

Sigaud made extensive use of the type terms muscular, respiratory, digestive and cerebral. Kretschmer added the study of character in relation to constitution, the conscious reactivity being obviously a part of the general constitutional makeup. To these and related classifications must be added those concerned chiefly with the functional status of the endocrine glands and finally the grouping of persons as primarily sympatheticotonic or vagotonic.

While we cannot review the recent contribution of Brown [9] at great length, we cannot but quote the pertinent conclusions that he has drawn from an elaborate and most convincing series of animal experiments that illustrate certain phases of constitutional resistance to disease. Brown wrote:

> The elementary conception of constitutional variation and its relation to disease which I have attempted to outline involves only one assumption, and that is that all functional activities of the body are either performed or controlled by organs and that the organs are provided in such numbers and amounts as are necessary for the performance of their appointed functions. One need not know the function of a single organ in order to show that persons differ from each other in respect of their organic equipment, or that they are persons and not standard machines or standard mediums for the growth of pathogenic microorganisms. It can be shown that variations in the mass and mass relations of organs are constantly occurring in response to demands made by the changing conditions of life and that these changes in organic constitution are accompanied by variations in chemical constitution, all of which may be confined within the usual limits of normal, for they are normal. It can also be shown that these differences and variations in physical and chemical constitution are associated with differences and variations in functional activity and susceptibility to disease or in the degree of natural immunity.

In studying our material, we have disregarded all anthropometric factors and have used only the grouping of slender, normal and heavy, as based on the weight/length ratio.

THE SLENDER (ASTHENIC) VERSUS THE HEAVY PERSON

It will be recalled that our two extremes based on such a classification showed, in general, the conditions set forth in table 1.

Does such a classification have any necessary relation to the concept of "sympatheticotonic type" or "vagotonic type?"

The Sympathetic Versus the Vagotonic Type.—When we examine the ten persons with the extreme "sympatheticotonic" reactions and the

9. Brown, Wade H.: Constitutional Variation and Susceptibility to Disease, Arch. Int. Med. **44**:625 (Nov.) 1929

ten with the extreme "vagotonic" reactions to epinephrine, as determined on the basis of the systolic reaction, we find the characteristics to be as shown in table 2. While the two classifications are by no means identical, we see that in both we deal with slender persons who have a

TABLE 1.—*Characteristics of Slender Persons and Heavy Persons of Extreme Type*

	Slender * (Weight/Length Ratio 1.87)	Heavy † (Weight/Length Ratio 2.32)
Capillary permeability	0.63 greater	0.57
K/Ca ratio	1.81 lower	2.08
Sugar	69.50 lower	73.80
Basal metabolic rate	+10.00 greater	+7.00
Muscle reaction	2.38 greater irritability	3.48
Epinephrine pulse pressure	+12 increased effect	+8.00
Co_2-combining power	+58.5 slightly more alkaline	54.4
Cholesterol	210 lower	225
Reactivity of skin		
Resistance of skin to electric current	0.66 higher	0.28
Reaction to ice	21 longer	19
Kromayer light erythema time	2.21 longer	2
Epinephrine wheal	18.8 smaller	20
Morphine flare	14.8 smaller	15.8
Thyroxin wheal	12.2 larger	11
Thyroxin flare	4.8 larger	3.2
Caffein wheal	19.2 larger	18
Caffein flare	2.8 larger	2.4

* Microsplanchnic type: phthisic habitus; asthenic habitus; linear type of Stockard; Pende presupposes an increase in basal metabolism; predominantly "sympatheticotonic."

† Megalosplanchnic type: "apoplectic" constitution; pyknic type of Kretschmer; lateral type of Stockard; Pende presupposes increased cholesterol, increased potassium, relative alkalosis and chloride retention; predominantly "vagotonic."

TABLE 2.—*Characteristics of Sympatheticotonic Persons and Vagotonic Persons of Extreme Type*

	Sympatheticotonic Group	Vagotonic Group
Capillary permeability *	69.1 increased	64.5
K/Ca ratio *	1.74 lower	2.04
Basal metabolic rate	+10.4 equal	+10.9
Muscle reaction	4 increased	2.3
Epinephrine pulse pressure *	+21.4 higher	—1.3
CO_2-combining power	54.6 lower	57.7
Cholesterol *	209 lower	218
Reactivity of skin		
Resistance of skin to electric current	0.41 equal	0.43
Reaction to ice *	23 longer	20
Kromayer light erythema time	1.72 shorter	1.95
Epinephrine wheal *	19.4 smaller	20
Epinephrine flare	9.4 larger	8.3
Thyroxin wheal.*	12 larger	11.4
Thyroxin flare *	4 larger	3.2
Caffein wheal *	21 larger	19.2
Caffein flare *	2.6 larger	2.4

* The reactions indicated by (*) are identical in direction in both the "slender" and the "sympatheticotonic" groups.

low K/Ca ratio, an increased vascular reaction to epinephrine, lower cholesterol, somewhat less reaction of the skin to epinephrine, and a greater reaction of the skin to thyroxin and caffein.

The "slender" person in contradistinction to the heavy person has, furthermore, an increased basal metabolic rate, a more irritable musculature with a slightly lower CO_2-combining power of the serum, higher

resistance of the skin to electric current and a longer Kromayer light reaction time.

The "sympatheticotonic" person in contradistinction to the "vagotonic" person has no difference in the basal metabolic rate, less muscular irritability and a lower CO_2-combining power, no difference in resistance of the skin to electric current and a slightly slower Kromayer light reaction time. The blood pressure is lower.

The Thyroid Type.—If we now compare the extreme "thyroid" type, we also have a slender person (ratio 201) with increased capillary permeability (ratio 72) and increased basal metabolic rate (+ 48), no change in the K/Ca ratio, but an increase in the total serum calcium and potassium; the skin blister time is shortened, the ice reaction time is rapid, the resistance of the skin to electric current is low and the epinephine wheal is small.

Pende [10] assumed that the sympathetic type is characterized by a state of defense and aggression (raising of blood pressure and pulse rate, glycogenolysis, etc.) the parasympathetic type by emphasis on intestinal and reproductive phases (glycogen formation, congestion of sex organs, etc.).

Goldstein, too, stressed the general catabolism, irritability and aggressiveness of the sympatheticotonic status as contrasted with the euphoria and hypomaniacal status of the vagotonic psychopathic person.

In this country Cannon, in particular, has studied the sympathetic nervous apparatus and recently demonstrated the nonvital character of these nervous impulses. Even the medullary chromophil tissue of the suprarenal glands in contrast with the cortical portions of the glands—is apparently without vital importance. After bilateral sympathectomy, emotional excitement does not cause erection of hairs, consistent increase of blood sugar, polycythemia, relative increase in mononuclear cells or marked rise of arterial blood pressure. Sympathectomized animals are sensitive to cold, and having lost the means of conserving heat, they lose heat more rapidly than normal animals. The basal metabolism usually falls somewhat after sympathectomy, especially after the cervical portion is excised. Though seemingly unessential under "normal conditions," it is of great service at times of critical emergencies when it adjusts the internal organs of the body for the use of the mechanisms responding to external exigencies.

The experiments of Cannon [11] and his co-workers are of particular importance because they demonstrate that the humoral factors (particularly the chemical) of integration of vegetative phenomena, after all,

10. Pende, N.: Riforma med. **41**:241, 1925.
11. Cannon, W. B.: Science **69**:502, 1929.

represent the older and underlying mechanism and must be considered in all of our medical problems, the nervous system being merely the more recent and less essential factor. As such, however, it may be the first to become disorganized and the first to give rise to clinical symptoms.

AUTONOMIC EQUILIBRIUM

The original concept of Eppinger and Hess of sympatheticotonic and vagotonic types has unfortunately been so impressed on the medical mind that more modern developments dealing with the autonomic status of the individual have found but slow acceptance.[12] It should be understood, as Ascher has so clearly stated, that the individual cells of the body are functionally distinct individuals, regulating their existence primarily through chemical means (this involves ionic, molecular, hormone and catalytic processes) and secondly, through nerve impulses, either central or vegetative.

Daniélopolu's Concept of Vegetative Tonus.—Daniélopolu[13] postulated three laws concerning reactions of the autonomic response which have an important bearing on the sympatheticotonic and vagotonic conception.

In the first place, substances that influence one factor also influence the other; i. e., they are amphotropic. The evidence for this has been accumulating for many years, and the literature has been reviewed repeatedly.[14]

With eye pressure, Daniélopolu demonstrated that the impulses proceed along two pathways, along the parasympathetic to the heart and along the sympathetic to the gastro-intestinal tract. Daniélopolu concluded that the vegetative tonus is maintained by amphotropic factors: one, peripheral and humoral, the other centrifugal, from the sympathetic and parasympathetic centers. When the tonus of one side is increased, the other automatically follows.

In clinical medicine, we frequently see, however, an apparent overbalance of the one system. Daniélopolu believed that the preponderance depends on the intensity of the impulses. In pharmacologic experiments, we know the importance of the size of the dose of the autonomic drugs. The effect on an organ depends on the general vegetative status of the entire organism, i. e., a minimal dose of epinephrine, which in the normal person results in parasympathetic stimulation (i. e., slowing heart rhythm and lowering of the blood pressure) causes increased blood pressure and pulse rate in the sympatheticotonic person; on the other

12. Editorial, Constitutional Vagotonia, J. A. M. A. **93**:1387 (Nov. 2) 1929.

13. Daniélopolu, D.: Klin. Wchnschr. **7**:1748, 1928.

14. Pick, E. P.: Arch. f. Physiol. **79**:183, 1920; Deutsche Ztschr. f. Nervenh. **106**:238, 1928. Sollman, Torald: Physiol. Rev. **2**:479, 1922.

hand, the dose which in the normal person causes increased blood pressure and pulse elicits a parasympathetic effect in the vagotonic person. These so-called paradoxic or inverted effects are, of course, well known. Finally, Danielopolu postulated a circular mechanism, the diagrammatic presentation of which we have reproduced.

Autonomic Equilibration and Increasing Amplitude of Response.—At this point, we should like to illustrate another fundamental phenomenon constantly met with in the study of autonomic regulation: first, the constant manifestation of the effort of the cell and the organ and the organism as a whole to maintain an equilibrium, disturbances of the balance being always followed by rhythmic and wavelike fluctuations in a direction opposite to the original change in status; second, the frequent manifestation of a progressive increase in amplitude in such rhythmic fluctuations following single impulses. We give charts for three typical experiments. The first shows the peripheral leukocytic fluctuations following bulbus pressure in the dog; the second, following irradiation of the skin. The third shows chemical fluctuations following a bacterial insult.

In a normal dog, a lymph fistula was made under local anesthesia. After reaction, bulbus pressure was maintained for seven minutes at the time indicated in chart 2. Peripheral leukocyte counts were made at frequent intervals, with determinations of lymph concentration, sugar, calcium and erepsin. The leukocyte count which reveals the fluctuations in the peripheral tonus (dilatation of vessels—leukocytosis; contraction, stasis, leukopenia) clearly indicates the rhythmic fluctuations of increasing amplitude initiated by this stimulus.

An almost identical picture is illustrated in chart 3. This dog had an exposure for seven and a half minutes to ultraviolet light applied over the abdomen, following recovery from incannulation of the thoracic duct under local anesthesia. It will be observed that the leukocyte curves show minor oscillations of increasing amplitude, with three chief periods of leukocytosis, the first 30 minutes, the second 75 minutes and the third 130 minutes, after the exposure. Calcium diminution occurs at approximately the same intervals.

In chart 4 we are able to illustrate an even more convincing picture with corresponding calcium fluctuations. In this case we deal with a bacterial insult. A pregnant dog was operated on under local anesthesia and an incannulation of the thoracic duct was made. After a period of observation following the operation, the continuous intravenous injection of a dilute suspension of *Bacillus coli* in saline solution commenced at 11:25 (first arrow on chart).

The curves at the top of the chart indicate the sugar level and the double line the K/Ca ratio (calcium level in black columns; potassium, in white columns).

The second group of curves indicate the rectal temperature and the volume of urine; the third, the lymph protein volume, the globulin per cent (in black) and the leukocyte curve. Inasmuch as the volume was sufficient to permit chemical analysis in five-minute samples, the actual fluctuation in the K/Ca ratio more accurately reflects the changes that occur in the tissues than has been possible in most of our other experiments.

It will be observed that the initial reaction was a slight increase in the calcium. A second and larger increase followed, reaching a maximum approximately sixty

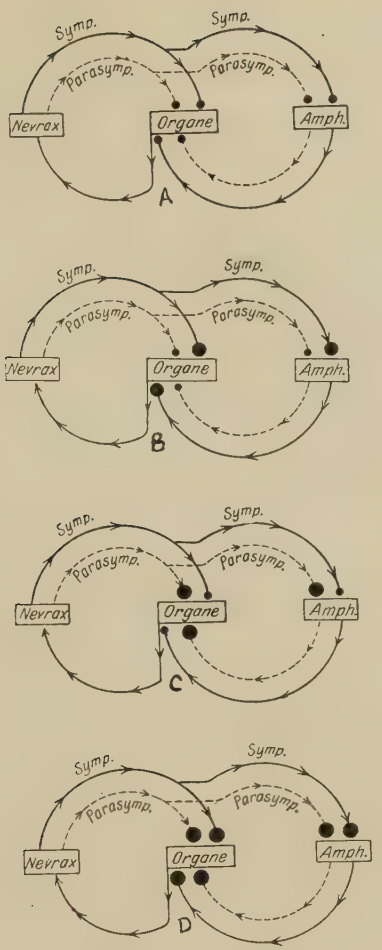


Chart 1.—Amphotropic circular mechanism of the autonomic tonus and its variations (from Danielopolu, D.: Klin. Wchnschr. **7**:1748, 1928). Diagram *A* indicates the normal status, i. e., equal sympathetic and parasympathetic amphotropism indicated by the equal size of the black dots.

Two factors are outlined: the peripheral amphotropic humoral factor (involving calcium, potassium, epinephrine, choline, pituitrin, cholesterol, etc.) keeping the sympathetic and parasympathetic nerve endings in a state of normal tone and maintaining a constant equilibrium. The organ itself, through the centripetal connections, acts to maintain the proper tonus of the vegetative sympathetic and parasympathetic centers. These centers again send centrifugal impulses via the sympathetic and parasympathetic tracts, which also act in maintaining tone in receptors. This forms the primary circle; a secondary one is associated. The glands of internal secretion, such as the suprarenal glands, which secrete amphotropic substances, have a dual vegetative innervation. We also know from Loewi's work that the organs give off amphotropic substances during functional activity. Grouped together, they may be called amphotropic secretory organs; in the charts they have been designated as "Amph." The impulses coming from the centers maintain a variable rate of activity in them, and this in turn regulates the peripheral factor.

B, sympathetic status, the sympathetic dot is heaver.

C, parasympathetic status, the parasympathetic dot is heavier.

D, amphotonic status, both dots are heavier.

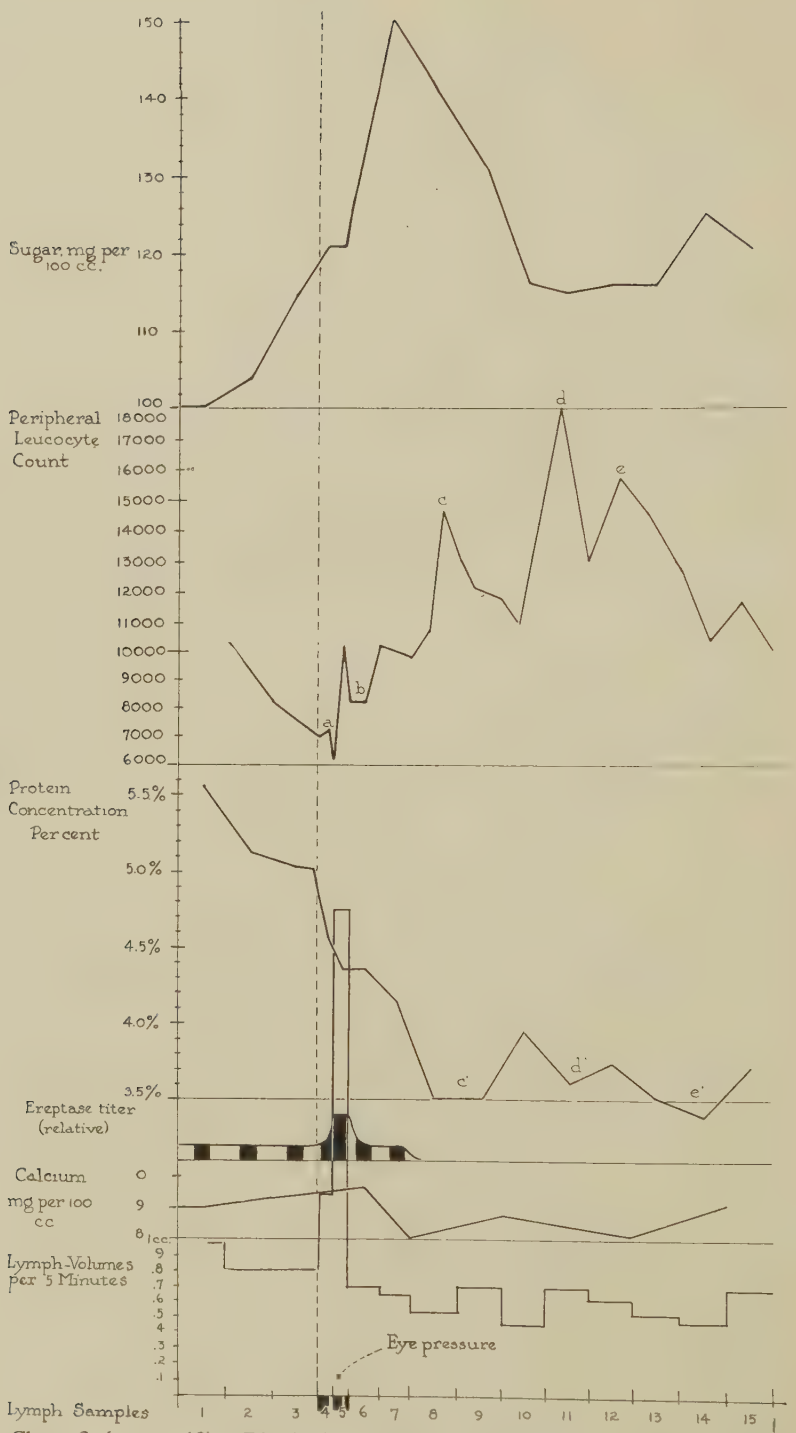


Chart 2 (exper. 18).—Rhythmic tonus waves (leukocyte curve) of increasing amplitude following bulbus pressure in dog.

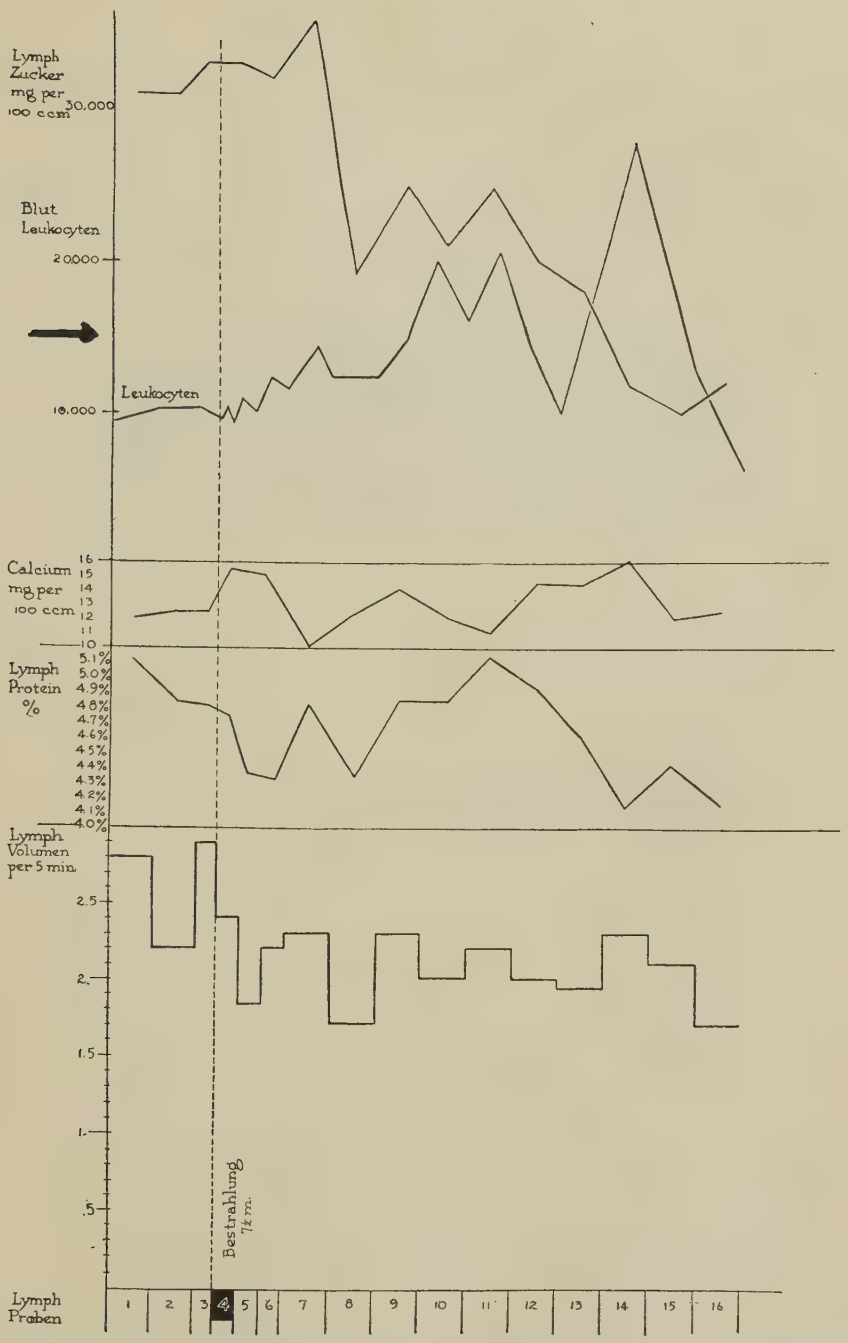


Chart 3 (exper. 2).—Rhythmic tonus waves of increasing amplitude following ultraviolet irradiation (from Petersen, W. F., and Von Oettingen, W. F.: Veränderungen der Lymphe beim Hunde nach Quarzlichtbestrahlungen, Arch. f. exper. Path. u. Pharmakol. **128**:160, 1927).

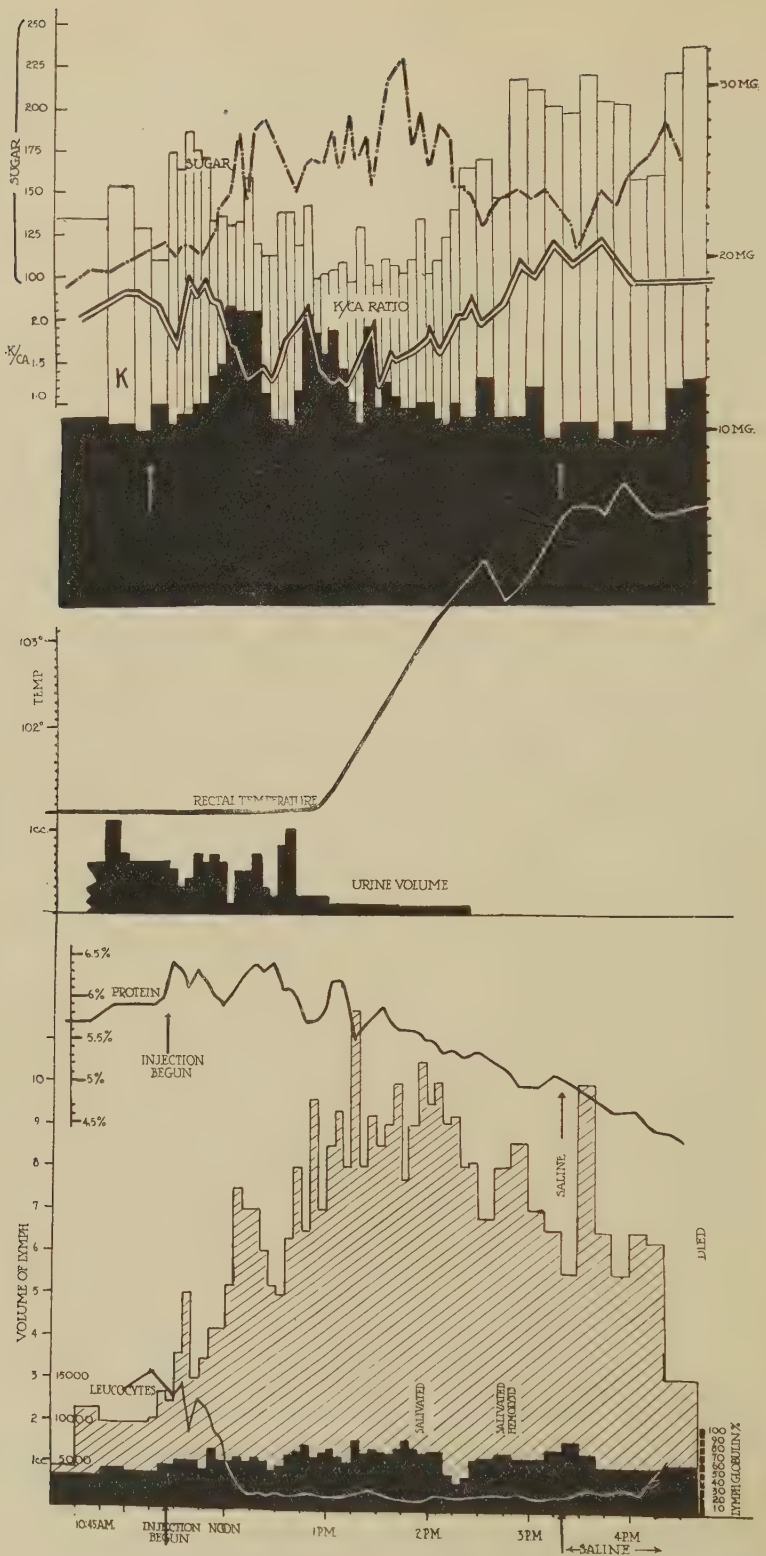


Chart 4 (exper. 18).—Typical fluctuations in the calcium and the potassium of the lymph with continuous injection of Bacillus coli (from Petersen, W. F.; Milles, G., and Müller, E. F.: Ztschr. f. d. ges. exper. Med. **60**:336, 1928).

minutes after the beginning of the injection, another after two hours and the fourth after two and a half hours. After that, the effects were effaced by a large amount of potassium coming from the injured red blood corpuscles. These chemical changes find their counterpart in the sugar curve, the lymph volume and the concentration of lymph protein. In this particular experiment, the leukocytes do not show a corresponding fluctuation, because the upset of the normal vascular splanchnoperipheral balance is so great that the peripheral region becomes fixed in a sympathetic status.

These fluctuations of alternating periods of stimulation and inhibition which find their expression in changes in the K/Ca ratio, in the sugar level, in lymph volume and in protein alterations, etc., form part of the splanchnoperipheral balance which Müller and one of us have discussed in various papers.[15]

In view of the foregoing observations, it is to be remembered that not only the general and local autonomic tonus is to be taken into consideration when the reaction of tissue is studied, but that one is dealing with a constantly fluctuating, labile condition and therefore the time element and the particular phase will always modify the response of the tissue.

Obviously, stimuli reaching a cell or organ when on the up or down grade, or at the peak, as contrasted with the trough, of a wave, may bring about diametrically opposite physiologic reactions. Tinel, Santenoise and Laurent [16] have made analogous observations in anaphylactic shock. They found that such shock always accelerates the preceding condition (status); and that then a reversal sets in. "Vagotonic" persons, for instance, have first increased excitability of the vagus; then a reversal sets in during which no further shock can occur. In the "sympatheticotonic," on the other hand, vagotonia is secondary, during which the patient is in a condition receptive to a new shock and to the continued effect of any circulating antigenic substance. With such a mechanism, one can more readily understand this reciprocal action of the autonomic tonus on shock and of shock on tonus.

Schilf's View of Autonomic Antagonists.—Before leaving the more general aspects of this subject, we shall have to review briefly the views of Schilf.[17] In line with the work of the Cannon school, Schilf pointed out that the older idea of a balanced nervous mechanism in the sense of a sympathetic-parasympathetic central antagonism, does not hold true for all tissues, there being a number in which only a sympathetic or only a parasympathetic innervation can be demonstrated. In the skin, for instance, we know of only sympathetic nerves for the sweat glands. Of greater importance for our problem, we know only of sympathetic nerves for the blood vessels. In only a limited region can parasympathetic (dilator) innervation be demonstrated, and the assump-

15. Müller, E. F., and Petersen, W. F.: Klin. Wchnschr. **5**:53, 1926.

16. Tinel, J.; Santenoise, D., and Laurent, O.: Bull. et mém. Soc. méd. d. hôp. de Paris **47**:471, 1923.

17. Schilf, E.: Klin. Wchnschr. **6**:29, 1927.

tion that, because sympathetic fibers are vasoconstricting, vasodilatation must be accomplished by parasympathetic fibers, is at the least, not established, indeed is probably fallacious. Schilf frankly stated that this problem of nerve control of vascular dilatation is still an unsolved problem, an opinion which is apparently shared by Stöhr.[17a] He emphasized that the organs predetermine their own course of action, and that we should stress organ reactions rather than attempt to force through a rigidly conceived idea of a vasomotor mechanism which actually is controverted by experimental facts. Particularly, the pharmacologic interpretation has done much to confuse the picture rather than to clarify it. The effect of a nerve impulse to an organ depends on the state of the organ to which that impulse is delivered. Schilf emphasized this, in particular, because "sick" organs react differently from normal organs.

Schilf's real contribution is his analysis of the fact that apparently antagonistic autonomic reactions (sphincterbladder mechanisms, for instance) can occur without nervous control and that such reactions are, from a broader point of view, not antagonistic but synergistic. So, too, for example, the control of temperature regulation, which, according to Cannon [18] is largely sympathetic. Here, again we are dealing with an apparent balance of sympathetic and parasympathetic impulses; apparently antagonistic, actually synergistic.[19]

A number of Russian physiologists and clinicians have reached conclusions similar to ours, among them Platroff.[20]

To this comes a more recent possibility that the sympathetic nerves are not only efferent, but also afferent, and may play a considerable rôle in periodic differences in the sensitivity to impulses; [21] and the contention of Viale [22] that the increase in the heart rate that follows cutting the vagi, is really due not to the deletion of inhibitory impulses, but to the increased secretion of epinephrine that follows. The correctness of such experiments must, of course, be first determined.

The discussion up to this point has, we believe, shown that we cannot arbitrarily select any one of the numerous factors that are involved in tissue activity and make it alone responsible for the clinical alterations that we see in every day practice. We are seldom justified in trying to establish purely endocrine imbalances; much less are we

17a. Stöhr, Philip, Jr.: Mikroskopische Anatomie des vegetetiven Nervensystems, Berlin, Julius Springer, 1928.

18. Cannon, W. B.: Tr. A. Am. Phys. **44**:41, 1929.

19. Petersen, W. F, and Müller, E F.: The Splanchnoperipheral Balance During Chill and Fever, Arch. Int. Med. **40**:575 (Nov.) 1927.

20. Platroff: Russk. Klin. **5**:3, 1926.

21. Förster: Schless. Gesellsch. f. väterland. Kultur, Breslau, abst. Klin. Wchnschr., Feb. 1, 1929.

22. Viale, G.: Boll. d. Soc. ital. di biol. sper. **2**:54, 1927. Smirnow, A. J., and Schinoky, W. F.: Ztschr. f. exper. Med. **55**:24, 1927.

justified in trying to establish a purely nervous imbalance. We might do best by following Bergmann and speaking of certain groups of patients as "vegetatively stigmatized," and we should definitely discontinue regarding only the readily observable smooth muscle reactions as criteria of systemic autonomic change. The smooth muscle, with its tonus, represents primitive contraction; the twitch of the voluntary muscle appears much later. But this tonus requires little oxygen; it is a vegetative phenomenon regulated by the bio-electric (ionic) means. Later, we superimpose vegetative and voluntary nerves, as well as the specialized amines and vegetative poisons, epinephrine, histamine, choline, etc., which can obviously act, as Langley suggested, directly on the cell membranes by changing colloidal structure, not necessarily on the nerve endings.

And if, in clinical parlance, we continue to use the term "sympatheticotonic" or "vagotonic" in lieu of the broader one of "autonomic dysfunction" or "vegetative stigmatism," we should have clearly in mind the many reservations which we have indicated.

The entire field of the "autonomic nervous system" has been thoroughly reviewed by Kuntz;[23] or one may consult the older book of Müller.[24] The more clinical "Vagotonies, Sympathicotonies and Neuritonies" by Guillaume[25] also offers much detailed information.

THE CHEMICAL EQUILIBRIUM

In the preceding discussion, we have traced the changes which have taken place from the original concept of functionally antagonistic sympathetic and vagus centers with resulting sympatheticotonia and vagotonia, to the present view with its emphasis on the autonomic status of the periphery. In the peripheral organ, we have already seen the presumptive influence of its milieu, its hormone content, its chemical equilibrium, etc., in determining local autonomic tonus and have also made note of the possibility of the effect of remote organs on such local tonus.

Rôle of Calcium and Potassium and the H-Ion Concentration.—The interest in the chemical phase goes back to the work of Jacques Loeb, who first emphasized the importance of the ions, particularly of calcium and potassium ions, in the control of cellular functions. The more recent and intensive cultivation of the field, particularly the application to clinical problems, comes from the school of Krause. Thus, Zondek,[26]

23. Kuntz, Albert: The Autonomic Nervous System, Philadelphia, Lea & Febiger, 1929.

24. Müller, L. R.: Die Lebensnerven, ed. 2, Berlin, Julius Springer, 1924.

25. Guillaume, A. C.: Vagotonies, Sympathicotonies and Neurotonies, ed. 2, Paris, Masson & Cie, 1928.

26. Zondek, S. G.: Klin. Wchnschr. **2**:382, 1923; **3**:707, 1924; **4**:905, 1925; Die Electrolyte, Berlin, Julius Springer, 1927.

after calling attention to the activity of ions on colloids in influencing their dispersion, hydration, etc., stressed the fact that two balances are of greatest physiologic importance, the H-ion concentration and the K/Ca ratio.

In general, we may accept the following:

With cellular activity, the calcium concentration of the cell membrane is diminished. Calcium leaves the cell, and there is a relative increase in potassium in the cell. The cell is more permeable, the protein becomes hydrated.[27]

From this stage of activity, as one pole, the opposite extreme, of rest, is reached, with apparently a relative increase of calcium at the cell surface, relative impermeability, dehydration, etc. Calcium and potassium concentrations are therefore indicative of the swing of the pendulum of cellular activity (Osterhout;[28] Lillie[29]).

These changes are cellular changes. They may be initiated by external impulses, a nerve impulse, for instance; the tone, however, will depend on a mechanism such as Danielopolu described. The concentration of either calcium or potassium in the serum may mirror the cellular change; but it must be clear that the serum levels do not necessarily change the reactions of the cells. The alteration of ionic concentration may ultimately bring about an abnormal vegetative reaction, but we may, and frequently do, find unipotential autonomic reactions without a corresponding consistent blood chemical picture.

The temptation is great to associate certain effects brought about by the increase of ionic concentration with definite autonomic nerve tonus; for instance, calcium with sympathetic effects, and potassium with vagus effects.

This association has been an outcome largely of clinical observations with injections of epinephrine hydrochloride. In the analysis which we present of our material on the basis of the epinephrine reaction, we have clearly shown that, while our outstanding "sympatheticotonic" persons had a lower K/Ca ratio (i. e., have relatively less potassium) than the outstanding "vagotonic" persons, there are many exceptions to the rule. But the fact that we find many exceptions to the rule, as did Brems,[30] and the fact that Jendrassik and Czike[31] could find no constant correlation at all between the reaction to epinephrine and the K/Ca ratio do not for a moment vitiate the importance of the ion balance for these autonomic alterations. We must not forget that the epinephrine

27. Zondek, S. G.: Biochem. Ztschr. **132**:362, 1922.

28. Osterhout, W. J. V.: Injury, Recovery and Death in Relation to Conductivity and Permeability, Philadelphia, J. B. Lippincott Company, 1922.

29. Lillie, Ralph: Protoplasmic Action and Nerve Actions, Chicago, University of Chicago Press, 1923.

30. Brems, A.: Acta med. Scandinav. **66**:207, 1927.

31. Jendrassik, L., and Czike, A.: Klin. Wchnschr. **6**:1521, 1927.

acts on the cell membrane—peripherally; the reaction of the cell depends on its status, tonus; i. e., on the ionic condition of its surface membrane. The relative ionic concentration of calcium and potassium in the adjacent cell fluids, quite apart from the blood, is only of secondary importance. Furthermore, all of our results and those of numerous others are estimated as total calcium and probably give a picture far different from the actual ionic calcium available.

Confusion of the Terminology Involved.—We must keep in mind, furthermore, that cell membranes are interposed between the cell protoplasm and the blood stream.

With a Donnan equilibrium here established, the amount of nondialyzable ions combined with protein on both sides of the membrane and the total amount of protein becomes of greatest importance.[32] We have shown by actual experiments (see chart 4) that with cell stimulation, calcium is liberated from the cell protoplasm and potassium there increased—corresponding to the time of vascular dilatation of the organ and therefore to a presumptive vagotonic status of the capillaries and tissues. This would mean that if we now use the term "vagotonia" as denoting a condition of tissue activity with capillary dilatation and increased permeability, then the blood stream should contain more calcium and relatively less potassium.

Actually, Kylin [33] found the "vagotonic" person, as clinically defined, to have more potassium and less calcium (higher K/Ca Ratio), and we, too, in using this clinical classification, can but confirm this.

Dresel [34] assumed that the blood of the "vagotonic" person is more alkaline and contrasts the resulting ionic states as follows:

Vagotonic Status	*Sympatheticotonic Status*
Tissues alkaline: little calcium-colloid, much potassium-colloid	Tissues acid: much calcium-colloid, little potassium-colloid
Blood alkaline: little ionized calcium, much bound calcium, little potassium	Blood acid: much ionized calcium, little bound calcium, much potassium

Accordingly, the "vagotonic" person should have a low K/Ca ratio, the physiologic effects being modified, however, by differences in ionization.

What we are actually facing here is merely a difference in definition. The clinical grouping of "vagotonic" does not define a person whose metabolism is increased and whose capillaries are permeable and dilated. This we should expect if in the vasomotor definition "dilatation" is synonymous with the "vagus effect." On the contrary, the clinically

32. The capillary endothelium is permeable for proteins when stimulated.

33. Kylin, E.: Deutsches Arch. f. klin. Med. **149**:354, 1925; Die Hypertoniekrankheiten, Berlin, Julius Springer, 1926.

34. Dresel, K.: Klin. Wchnschr. **1**:1601, 1922; Klin. Wchnschr. **3**:311, 1924.

"vagotonic" person has a lower rate of metabolism and less permeable capillaries. Dresel was correct in theory, Kylin in practice. We can illustrate this further in the chemical changes of sleep.[35]

Here we deal with a "vagotonia," even in decerebrate animals. There can be no doubt about the general condition of tissue rest; during this time, calcium diminishes in the blood and increases in the tissues and the potassium values show the reverse. The greater frequency of attacks of asthma and angina pectoris, the occurrence of pavor nocturnus, Pende ascribed to the vagus preponderance at night.

Clinical Grouping of Vagotonic and Sympatheticotonic Persons.—We have discussed this at some length to bring out the fallacy of our present classification of "sympatheticotonic" and "vagotonic." It should be given up, unless we are clearly cognizant of the various implications.

When we have spoken of the sympathetic status, we have always indicated the state of tissue rest: contracted vessels, calcium accumulation, dehydration.[36] When we have spoken of the parasympathetic status, we have indicated the state of the tissue with dilated capillaries, tissue activation, calcium dissimilation, hydration. When we have used the terms "sympatheticotonic" and "vagotonic," we have designated the clinical states as commonly interpreted.

And this brings up another apparent inconsistency. When smooth muscle contracts, the obvious inference is that the muscle tissue is active (it may contract, of course, with either sympathetic or parasympathetic stimulation), but actually during contraction the capillaries are also contracted, their endothelium is less permeable, metabolic processes are slowed, less energy is supplied. With relaxation comes dilatation of the vascular bed and increased permeability. Relaxation must, therefore, if we wish to be consistent, be the period of metabolic activity, i. e., the parasympathetic status in the sense that we have used it.

Now, it happens that when epinephrine is injected in small doses, the blood vessels dilate and the endothelium becomes more permeable. It is a true parasympathetic status of the tissues. With larger doses, the vascular musculature contracts, and the endothelium becomes less permeable. These are direct cellular effects and take place presumably without nervous mediation. This is a true sympathetic effect. But the many other effects initiated at the same time by the large dose of epinephrine result in a most complex picture.

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35. Fischer, H.: Biochem. Ztschr. **193**:169, 1928.

36. If the sympathetic status with contracted vessels occurs for a long period of time with a resulting stasis in the capillaries, it is possible that the cellular metabolism of the region will show a condition far different from "rest," i. e., rather an asphyxial stimulation. Such states may presumably occur in the peripheral tissues during a chill.

Of course, Zondek [37] was careful to state that the vagus effect is like the potassium effect; he never insisted that the two are identical, although, in general, it is assumed that the nerve impulse makes use of the ions in upsetting the membrane equilibrium. With this consideration, one can understand why in certain clinical conditions—urticaria, for example—the calcium level may be normal and yet the administration of calcium be, at times, useful, at other times, without effect. We can understand why the level may be constant—and it is one of the most firmly held of the balances, as Kroetz [38] has shown, with a negative balance; i. e., cells may be losing calcium, but the level remains the same, as Aub [39] and his associates have so clearly demonstrated in exophthalmic goiter. And we can understand why the level may be low in the blood, while the relation in the cell membranes is at its proper level.

Rôle of Cholesterol.—There seems to be some basis for the belief that cholesterol is involved as an intermediary in the ionic autonomic mechanism that we have been discussing,[40] and here again we are dealing with a confusion resulting from the presumable effects of cholesterol as a component of the cell membrane and cholesterol free in the blood stream. It is, of course, possible that an increase in the cell membrane can be present at the same time that we have an increase in the blood stream. The possibility also exists that with an active exchange going on between the two, high membrane content may be associated with low plasma content and vice versa. Just as with the ionic balance, the membrane relations present great complexity, with innumerable physical and chemical differences, free and saponifiable forms and the ability of the blood proteins to form protective colloids all influencing the ultimate balance. Mjassnikow [41] definitely associated the increase in blood cholesterol with hyperasthenia, not only in the apparently normal condition, but in the associated diseases, of this constitutional type, i. e., gout, obesity, hypertonia, asthma, hay fever, gallstones, etc. This cholesterol increase appears to be true for our "heavy" group, as well.

But Dresel and Sternheimer [42] definitely placed cholesterol in the sympatheticotonic group, counterbalanced by lecithin as a parasym-

37. Zondek, S. G.: Klin. Wchnschr. **6**:1951, 1927; footnote 26, second reference.

38. Kroetz, C.: Verhandl. d. deutsch. Gesellsch. f. inn. Med., Kong. **40**:91, 1928.

39. Aub, J. C.; Bauer, W.; Heath, C., and Roper, M.: J. Clin. Investigation **11**:97, 1929.

40. Westphal, K.: Ztschr. f. klin. Med. **101**:545, 566, 584 and 603, 1925.

41. Mjassnikow, A. L. : Ztschr. f. klin. Med. **105**:228, 1927.

42. Dresel, K., and Sternheimer, R.: Klin. Wchnschr. **4**:816, 1925.

pathetic agent. Glaser [43] discussed some of the relations in arteriosclerosis and found, as had Wacker and Hueck,[44] that the injection of epinephrine hydrochloride increases the amount of cholesterol in the serum. A complete discussion of the literature would be superfluous at this time. We merely mention the probable rôle of these lipoids in the chemical and physical equilibrium that is involved in the autonomic background.

THE SKIN

Its Autonomic Importance.—Among the vegetative organs concerned with our immediate relation and adjustment to the outside world, none is of greater importance than the skin; it is unfortunate that it has been largely ignored by the physiologist, perhaps, because in his preoccupation with the experimental animal, he has failed to realize how far different the human skin is in its reactivity from that of any of the lower animals; perhaps because he has regarded the skin merely as a protective mechanism—the "overcoat" with which Engman has chided the dermatologists for their narrow point of view.

As a matter of fact, the skin is the reactive membrane for the whole organism, just as the cell membrane is for the individual cell, and with almost as many important and sensitive receptors and reactive possibilities. Clinical observation has always recognized the interrelation of the skin and the deeper tissues. The so-called antagonism of visceral and skin tuberculosis and syphilis is one example. So, too, is the protective immunity established by the exanthems; and the tradition that a good reaction of the skin protects against internal complications in the same group of infections is established folklore. More recently, the rôle of the skin in allergy and the therapeutic possibilities incidental to stimulation of the skin have raised the clinical interest and aroused considerable investigative curiosity. Müller and Delbanco [45] developed the idea of the skin as a vegetative sense organ and in line with von Groer [46] emphasized the skin as a mediator of autonomic regulations by virtue of both its chemical and its physical potentialities.

As is well known, the latitude of the adaptability of the skin to an insult or to a change in environment is great, must of necessity be great, because on it depends the life of the whole organism.

We should therefore like to develop the subject of the importance of the skin and its autonomic tonus in more detail and shall use bacterial invasion as an example of the effect of an abnormal external insult.

Local Resistance.—The sum total of the processes involved may vary from the normal physiologic responses, or what may be termed

43. Glaser, F.: Klin. Wchnschr. **6**:2377, 1927.
44. Wacker, L., and Hueck, W.: München. med. Wchnschr. **60**:2097, 1913.
45. Müller, E. F., and Delbanco, E.: Dermat. Wchnschr. **87**:1348, 1928.
46. von Groer, F.: Klin. Wchnschr. **6**:96, 1927.

"local tissue resistance," all the way to the severe inflammatory reactions elicited when certain organisms or biologically active toxic substances penetrate the superficial layers. The human skin, as we have pointed out, is much more reactive both specifically and nonspecifically than the skin of other animals.

The inflammatory reaction differs in degree from the normal physiologic response, the direction of the change is apparently uniform at the onset in both cases. Both the "local resistance" of the normal and undamaged tissue and the inflammatory resistance depend to a marked degree on the preexisting vegetative status of the tissues.

In order to maintain local resistance of the tissue an unaltered function of the cellular elements is the prime requisite; the second is an undisturbed replacement of the energy requirements during the course of normal metabolic processes. This involves a definite orientation of the autonomic apparatus of the involved tissue, so that the full development of tissue function and energy supply can be maintained.

Certain cells, particularly those that are to some extent free from cell complexes and organs (reticulo-endothelium and the resting wandering cells of Maximow), are more independent in their adaptability to changes in the environment in so far as they seem less subject to the influences which are operative when cell groups are involved.

On the other hand, in the organized tissues, every reaction of one organ involves more or less directly certain fundamental correlations with all the other organs and tissues. Brown's [9] work makes this interrelation evident. Remote organs, under conditions of stimulation, may then act either as accelerators or inhibitors of the function of other organs, whereby the adaptability of a remote zone may be enhanced or retarded.

The law of Dastre and Morat and our own experiments with the splanchnoperipheral balance of the organs show this clearly. If, for any reason, we observe a sudden increase of activity of the abdominal organs with increased vascularity of the region, there is not only a diminished amount of blood in the peripheral vascular bed, but also a diminution in the functional capacity of the peripheral organs associated with synchronous contraction of the vessels.[47]

We have already touched on the autonomic vascular mechanism involved, in connection with the paper of Schilf. We shall here limit ourselves to the question how far such alterations (which are constantly occurring under physiologic conditions) influence the organs and tissues

47. Fremont-Smith, F.; Morrison, L. R., and Makepiece, A.: Proc. Am. Soc. Clin. Investigation, May 6, 1929; abstr., J. Clin. Investigation **7**:489, 1929. Smith, Morrison and Makepiece have recently made observations on the capillaries during chill and find a complete stasis in all visible capillaries due to the constriction of the terminal arterioles.

with a possible loss of the local resistance of the tissue and predisposition to disease.

Herpes and Splanchnoperipheral Balance.—On the skin, in the nasal mucous membrane, and in the gastro-intestinal mucous membrane, pathogenic organisms live without further penetration, that is, until at some time a slight trauma, a "cold" or some other indisposition leads to local infection. With mechanical injury and its obvious disturbance, the lowering of the resistance of the tissue is easily understood. It is much more difficult to understand the other types of susceptibility, the appearance of a labial herpes for instance, with a sudden onset of fever. We know its pathognomonic interest and the enormous spread occasionally seen in association with the chill of an infection with *Bacillus coli;* we also know the nasoparasitic character of herpes virus.

The ubiquitous virus previously present in the adjacent surface of the skin suddenly penetrates the superficial layers and, from the clinical point of view, becomes virulent at the time of systemic reaction incidental to the generalized disease. The virus, having once penetrated, meets with further resistance in the form of local inflammation, the intensity of which is usually sufficient to check the further spread.

This picture is a typical example of the transition of a previously latent organism to full virulency as the result of the failure of local resistance of tissue. The question as to the cause of such failure with the onset of the chill and high temperature is of far greater interest than that involved in the mechanism of the infection of the pelvis or uterus with *B. coli* in septic abortion. Other herpetiform invasions are apparently related to similar processes: the herpes infection of the skin in certain periods of the menstrual cycle, and in certain persons during acute indigestion, etc.

The cause is always the same. A sudden and intense increase of activity in the splanchnic region involving marked increase in the vascular bed and increase of the secretory function reflexly involves a change in the peripheral tissues. The change includes a diminution in the size of the vascular bed and a reduction of cellular activity. The periphery becomes less capable of reaction to external stimuli for the reason that reactions which under normal conditions are associated with increased vascularity and increased metabolic cell processes are either diminished or do not make their appearance.

A second possibility must be considered. The stasis of the peripheral capillaries may be of sufficient duration to bring about injury of the more superficial epithelial cells—cells that normally are undergoing necrobiosis. This dysfunction incident to the stasis may be sufficient to account for the penetration.

Such alteration of the distribution of the blood takes place in all conditions associated with fever. A similar redistribution in the vascular

bed together with an increase of the secretory function of the stomach and other large glands of the abdominal region occurs in varying intensity during the menstrual cycle, during migraine and even during digestion, more evident in certain persons, when we see it as part of the "Widal hemoclastic crisis."

The cause of this abdominal splanchnic dilatation may vary in individual cases, but the reaction of the organs and the vessels in the splanchnic region is fundamentally the same. It is unidirectional, and it is associated with peripheral constriction made apparent in the pallor of the skin, with headache, with nausea, etc. In the chill of an infection with *B. coli,* one can observe the most intense form of this splanchno-peripheral change. The enormous increase in activity of the liver which results from the systemic invasions is associated with a decreased flow of blood at the periphery and a diminution of all peripheral cellular function. It is this latter change which is of the greatest practical importance.

Heat radiation and sweat formation are clinically familiar to us. Their inhibition, even if transient, is part of the mechanism that causes fever, because the dissipation of heat produced by the increased activity of the splanchnic organs is thereby checked. Only when, with gradually diminishing activity of the liver, the correlated inhibition of the autonomic functions of the skin is lessened, does the temperature begin to fall. During the menstrual cycle, similar conditions may prevail even though the clinical symptoms are less apparent. Here, too, one finds minor fluctuations of temperature that have the same physiologic basis, though here without infection.

Local tissue resistance, which is most impressive in the skin, is subject to the same inhibitory influences. Reactions of the skin associated with increased resistance to infection are hard to recognize. It is true that our clinical experience indicates that a skin or a mucous membrane with good circulation is less apt to become infected, and that healing takes place more rapidly under such conditions. This might be apparent, too, from the relative freedom of the exophthalmic patient from infections of the skin.

Inhibitory influences on the skin, with diminution of its autonomic adaptability, also become apparent only when every day demands are not met in the normal fashion, for example, when one has a virus present and finds that with lowering of the local tissue resistance, the virus is enabled to penetrate into the deeper tissues.

It is of secondary importance whether such an inhibition takes place primarily through nerve impulses, through alteration of the metabolism or through endocrine alterations which secondarily lower the resistance toward the infections.

We [48] have previously noted definite autonomic influences on the skin of women during the menstrual cycle. In the absence of a potential virus on the skin, these alterations are clinically innocuous because, practically, one is dealing only with a susceptibility toward infection. Only when one is dealing with a potential infection, as in persons harboring the herpes virus, does the periodic depression of resistance become apparent.

Respiratory Tract.—In the nasopharynx, similar autonomic influences become apparent. In chill and in high fever, the mucous membranes of the mouth and the nose are dry because the cell functions of the mucous membranes are definitely depressed or inhibited. The coated tongue is a manifestation of the same influences.

Glands and mucous membranes are in themselves uninjured; it is only their functions which are diminished during the time of fever. Despite urgent need and mechanical stimulation through chewing and sucking and contact with food, the formation of saliva is inhibited because of the vegetative contraction of blood vessels, as well as the vegetative inhibition of the cell functions. The same condition holds true for the hunger sense. The diminution of contractions that we [49] have demonstrated for the stomach during this time is part of the picture of diminished appetite (the opposite vegetative orientations of salivary glands, mucous membranes and tongue, on the one hand, and of stomach, liver, etc., on the other, are particularly marked in these cases, as we have shown previously). The stomach during this time is under a condition of stimulation which leads to a considerable secretion of a strongly acid stomach juice.

Other infections of the mucous membranes besides herpes are well known during fever, for instance, the inflammatory reaction of the upper part of the respiratory tract, as well as of the conjunctiva. Such inflammatory reactions are by no means to be regarded as part of the primary infection, but are merely manifestations that these tissues for the time being have lost their resistance either partially or entirely, resistance which under normal conditions would be more than able to cope with every day irritations. Here, for instance, could be mentioned the conjunctivitis occasionally seen with the flare-up of a localized pulmonary tuberculosis, so characteristic that it may be regarded as a distinct symptom of activation.

We shall show later on that the exanthems of the acute exanthematous infections (scarlet fever, measles) only become possible because

48. Petersen, W. F., and Milles, George: Relation of Menstruation to Permeability of Skin Capillaries and the Autonomic Tonus of Skin Vessels, Arch. Int. Med. **38**:730 (Dec.) 1926.

49. Müller, E. F., and Petersen, W. F.: München. med. Wchnschr. **74**:531, 1927.

the skin and the mucous membranes have a diminished resistance toward the circulating toxin. Müller, Metz and Myers [50] demonstrated such a pathogenicity for one exanthematous disease due to a known toxin, namely, the arsenical dermatitis following arsphenamine.

Even the occurrence of halitosis in severe infections is due to the lessening of cell activity in the mucous membrane of the mouth, with diminution of the bactericidal power. The idea that the fetor is of stomachic origin is incorrect, for the growth of bacteria in the stomach is not increased during fever, though the bacterial flora may ascend to the higher levels of the gastro-intestinal tract, as has been demonstrated by Arnold and Brody.[51] As a matter of fact, the stomach contents, when removed, have no such fetid odor. Soor paradentosis, caries and the pityriasis versicolor of the cachectic patient have a similar origin in so far as the loss of the resistance of the tissue makes possible the infections named. The loss of hair and the impairment of the growth of the nails give further evidence of the peripheral vascular disturbances.

Before we enter into a discussion of similar changes in the other organs, we must discuss for a moment those reactions which serve for the protection of tissue when toxic substances or a virus have entered the skin and the mucous membrane. We characterize them as inflammatory. Intensity of change, and this in relation to the protection of tissue means the effectiveness of change, also depends on vegetative orientation of the tissue as such. Examples of such influences are well known. With the onset of fever—let us say the sudden onset of an angina—the exudate of a gonorrheal infection ceases for a time. The formation of pus in a sterile turpentine abscess during a fever starts after defervescence; all evidences that an autonomic influence is of paramount importance in local inflammatory processes.

The work of Kauffmann [52] and of Petersen [53] presents further examples. Particularly, the work of Kauffmann with cantharides blister during the course of lobar pneumonia seems to us of particular significance, because Kauffmann carried out his experiments without considering the autonomic orientation in its influence on the metabolism and reactivity of the tissues. During the course of the febrile stage of pneumonia, he observed a decided impairment of reaction. He said:

> The exudates are peculiarly poor in the cellular elements. Among the cells present lympho-histiocytic elements are completely absent, as are also eosinophile cells, so that the exudate consists practically of neutrophile leukocytes. But even

50. Müller, E. F.; Metz, G. P., and Myers, C. N.: Arsenic Lesions of the Skin, Arch. Dermat. & Syph. **15**:186 (Feb.) 1927.

51. Arnold, L., and Brody, L.: Am. J. Hyg. **6**:672, 1926.

52. Kauffmann, F.: Krankheitsforschung **2**:372, 1926.

53. Petersen, W. F., and Willis, D. A.: Capillary Permeability and the Inflammatory Index of the Skin in the Normal Person as Determined by the Blister, Arch. Int. Med. **38**:663 (Nov.) 1926.

the immigrative cell elements so represented are increasingly diminished in the more severe disease processes. It is only with the crisis—when the inhibitory influences on the skin have disappeared, that inflammatory irritability and particularly the intensity of the cellular processes again increase.

In this work with the cantharides blister, Kauffmann therefore described the dependence of the inflammatory reaction on the vegetative orientation. Some years ago, Müller [54] pointed out that every collection of leukocytes was associated with a dilatation of vessels. Such dilatation is inhibited during a period of general reaction to infection. Herein, just as in the inhibition or diminution of the mobilization of tissue cells in the inflammatory exudate, we can recognize the negation of this phase of tissue protection of the skin at times when the center of metabolic activity of the body has been transposed to the internal organs.

Gastro-Intestinal Tract and Change of Temperature.—The reversal of such vegetative orientation can also be established. Arnold [1] showed that when the blood vessels of the skin and the peripheral tissues are active, the bactericidal properties (that is the self-protection of the tissues) in the gastro-intestinal tract, particularly of the duodenum and the upper jejunum, are diminished. Man, as well as animals, exposed to heat and high humidity show, not only a coincident diminution in the secretion of the gastro-intestinal fluids, but a diminution in the normal response of the gastro-intestinal tract to food. If one examines dogs in superheated rooms, bacteria are found passing the stomach and duodenum practically in 100 per cent of the cases, whereas in the animals kept under normal conditions of temperature the bacteria are killed. If one feeds such overheated animals meat poisoned with enteritis toxin, the animals die, whereas animals kept at normal temperature or a cool temperature survive. If one measures the organic function of these animals in terms of stomach and bile secretion, following ingestion of poisoned meat, then one observes a marked and occasionally a total inhibition in the animals kept too warm and an enormous reaction in the control animals. In the human being, we also have observed this diminution with external heat as contrasted with normal temperature and a correspondingly increased reaction at the time of actual chill. The susceptibility to gastro-intestinal infection increases notably at times of increased external temperature. This is not only the case when infected food or pathogenic organisms pass in fully virulent form through the stomach to the gastro-intestinal tract. Even the normal gastro-intestinal parasitic flora is no longer indifferent under these conditions. Thus, Arnold [55] showed that with increasing

54. Müller, E. F.: München. med. Wchnschr. **69**:1506, 1922.

55. Arnold, L.: Am. J. Hyg. **8**:604, 1928.

external temperature the flora changes its character, as well as its range. Characteristically, the lower gastro-intestinal flora invades the upper region of the gastro-intestinal tract. Similar conditions underly the manifestations of gastro-intestinal morbidity in populations at the beginning of the warmer periods of the year or in persons who go from cold to tropical climates. With the associated increased activity of the periphery of the body, the functional capacity of the abdominal organs is diminished.

This, too, is not necessarily dependent on the actual height of the external temperature, but rather on the reactivity of the skin and the lungs at the time, and on the autonomic impulses that under those conditions leave the periphery and influence the gastro-intestinal tract and the abdominal group of organs, in general. The decrease of resistance of the gastro-intestinal wall—in other words, the increase of susceptibility—in warm climates and in the hot summer is therefore most apparent in the unacclimated persons, that is, with sudden and unaccustomed changes, rather than in persons who gradually accustom themselves to higher temperatures. This point is of epidemiologic importance for a variety of gastro-intestinal infections, as well as for tropical diseases.

In the liver, too, the local immunity of the parenchyma is clearly dependent on the autonomic orientation of the tissues and is only effective when inhibitory impulses are not predominant.

The normal increase in activity of the liver in chill and fever has been previously described in some detail.[56] Secretion of lymph and bile increases tremendously and with it vascularization, function and cell permeability. The marked increase of the permeability of the cells and tissues, in general, does not involve a necessary penetrability for all substances present in the blood. Despite continuous intravenous injection of living *B. coli* in the animal over experimental periods lasting for hours, the lymph of the thoracic duct remains free from bacteria. That is, the sterility of the lymph is constant as the function of the liver increases. On the other hand, bacteria are being constantly excreted into the bile passages. If such an experimental injection of *B. coli* is continued long enough (for ten, fifteen or twenty hours), one arrives at a time when the function of the liver is apparently rapidly diminished. At this time, the peripheral constriction of the vascular bed is also broken, and the animals show a peripheral hyperemia. In the liver, the vessels contract, the permeability of cell and tissue is diminished, as is the production of lymph and bile. At the time of this injury, red blood corpuscles appear in the lymph stream, proteolytic

56. Petersen, W. F.; Müller, E. F., and Boikan, W.: J. Infect Dis. **41**:405, 1927.

enzymes are markedly increased, the temperature falls, and some of the bacteria make their way into the lymph stream. Later this picture may be reversed.

Here, too, we see that the characteristic balance between the skin and the mucous membranes of the mouth, on the one hand, and the mucous membranes of the gastro-intestinal tract, on the other, may also influence the local resistance of tissue in other organs by means of a supererogated vegetative control.

These observations seem of certain importance in various directions, not only for the understanding of such processes as herpes, the infections of the mucous membranes of the mouth with parasitic invaders previously latent, and the catarrhal conditions of mucous membranes, in general, during infectious diseases and following chilling of the body surfaces, but for the understanding of gastro-intestinal manifestations in persons in unaccustomed warm climates, and of the status of the liver in the course of septic infections. From them we may be permitted to make certain deductions concerning the susceptibility of organs and tissues, in general.

The protection of normal tissues against an infection does not depend to any great degree on immune powers of the serum, but is, as every other function of the body, due to the cellular activity of the tissues and therefore is closely associated with the vegetative impulses and the vegetative status as particularly manifest in vascular alteration. One realizes, too, that the cellular tissue functions, on which local resistance depends, are controlled (as are all other functions of cells and tissues) in their responses and activity not only by the anatomic and functional activity of the individual elements as single cell organisms might be, but by certain limitations of their potential possibilities placed on them by more remote organic processes that directly influence the intensity of the vegetative orientation not only of the entire body, but of the local organs and tissues. It is possible, therefore, that with complete anatomic and physiologic integrity of the tissues, and despite the manifest danger due to the local infection, the local resistance of tissue may fail because it is inhibited through influences which, originating in remote regions, influence the local functional status. How this inhibition of functional response in the tissues may be brought about is clinically and practically unessential. At least two possibilities exist. Primarily, the diminution of function may be secondary to vascular dysfunction with an associated diminution of energy resources. Secondly, it may be directly imposed by the vegetative nervous impulses, or by chemical or hormone alterations acting on the blood vessels, as well as on the individual cells, either immediately or mediately.

The only fact that is of practical importance is that the local protection of the tissues, particularly those that have come in contact with

the surrounding world, is associated with and dependent on a superimposed vegetative orientation. Important is the knowledge that influences which may change the vitality of tissues, the functional capacity of the tissue and therefore the self-protective mechanism may remain objectively unnoticed, since they can be measured only in the end-result. In terms of relative resistance, they are perceptible only indirectly, that is, when functional inhibition has gone so far that the infection actually takes place.

It is not the mechanical integrity of the skin that offers the most effective protection, it is the vegetative condition of the tissue during which the adaptability of the cells can be developed to its maximum potential degree. It is seen that, on the basis of the splanchnoperipheral balance in the community of organ response, the more intense activity of the one group is balanced by a relative inhibition of the vital activity and capacity of another group, and that local resistance, as a measure of metabolic activity, as other functions, loses some of its potentiality under the influence of inhibitory forces. The local resistance of tissue is intimately bound up and dependent on local tissue elements and their functional capacity. With lowering of this functional capacity of the tissue, there occurs a lowering of the resistance of the tissue, irrespective of the origin of these inhibitory influences from without or from within, or of whether they are initiated by tangible organic changes or by psychic processes. The head cold, for instance, is not the result of a change of temperature to which one may have been exposed, but is the result of an individual difference in local resistance. Even in a severe draft with a considerable cooling, the temperature of the mouth, of the nasopharynx, of the musculature and of the joint cavities may remain approximately the same. With long continued intensive cold of the skin, of course, all the tissues and organs respond, the peripheral ones with a relative diminution of vascularity. We are therefore of the opinion (because of clinical observation) not only that articular rheumatism may be due to certain types of organisms, but that the joint membranes and the musculature have definite fluctuations of resistance against these invaders depending on the vegetative orientation of the moment. The Weber phenomenon is based on the fact that sudden displeasure or sadness leads to a diminution in the amount of blood in the periphery with a corresponding increase in the abdomen. But in psychic trauma, such as fright or fear or worry, a severe and long continued physical influence on the body can be brought about. In all of these one finds pallor of the skin, dryness of the mouth, loss of appetite, etc. One can readily see that the influences that make manifest many organic disturbances in association with psychic trauma do so because of the fundamental and underlying autonomic changes that we

have discussed in relation to the herpes virus. The organic changes depend, as this does, on the vegetative ability and adaptability of the local tissue.

EXOPHTHALMIC GOITER

Recently, Warthin,[57] in a discussion of exophthalmic goiter, reaffirmed his conviction that the underlying factor is constitutional, symptoms developing only as a result of abnormal reactions to stimuli which in a normal person would be met by physiologic adaptation. Oswald,[58] too, believed that the effect on the thyroid gland depends wholly on an instability of the nervous system in certain persons, an instability that Kessel, Lieb and Hyman [59] place in the myoneural junction. Warthin, furthermore, believed that "Graves' constitution" is associated with a "thymic-lymphatic" status and is characterized by hyperplastic primitive lymph nodes in the gland itself, which is involved in the disease only incidentally. Aschoff and Krehl both expressed similar views, and Miller [60] emphazied the probability of at least two active factors in the disease, one not identical with the substance that increases the basal metabolism.

There is a growing volume of clinical comment in agreement with this view.[61] Bram [62] tersely differentiated toxic adenoma by stating that here "the thyroid makes the body sick; in exophthalmic goiter (a constitutional disease) it is the body that makes the thyroid sick."

Our previous,[63] as well as present, series have made apparent a striking increase in capillary permeability in exophthalmic goiter, which, we believe, is basically associated with the clinical manifestations. Such an increase in permeability has been suspected as a result of the previous work of Eppinger and Hess. Gellhorn [64] has more recently proved the increase in permeability by direct experiments. Weil [65] drew the conclusion that the increase in permeability is to be correlated with, first, the increase in absorption and, second, the increased electrical conductivity of the tissues, and finally, with the increase in cell division

57. Warthin, A. S.: Ann. Int. Med. **2**:553, 1928.

58. Oswald, A.: Klin. Wchnschr. **4**:1053, 1925.

59. Kessel, L.; Lieb, E. C., and Hyman, H. T.: A Study of Exophthalmic Goiter and the Involuntary Nervous System, J. A. M. A. **79**:1213 (Oct. 7) 1927.

60. Miller, J. L.: Proc. Inst. Med, Chicago **7**:89, 1929.

61. Zondek, H., and Bansi, H. W.: Klin. Wchnschr. **8**:1697, 1929.

62. Bram, I.: M. J. & Rec. **129**:579, 1929.

63. Petersen, W. F.: The Permeability of Skin Capillaries in Various Clinical Conditions, Arch. Int. Med. **39**:19 (Jan.) 1927.

64. Gellhorn, E.: Das Permeabilitäts Problem, Berlin, Julius Springer, 1929, p. 341.

65. Weil, R.: Klin. Wchnschr. **8**:852, 1929.

observed in exophthalmic goiter. Weil found that thyroxin in small doses increases liver autolysis, which is due, presumably, to colloid chemical membrane changes with increased permeability. The clinical interest, as well as the physiologic interest, must therefore turn from the supposition that the effect is on the nerve endings as an intermediary. We are really dealing with a direct membrane change.

Dresel,[66] who also observed an increase in amino acids in liver autolysis following the injection of thyroxin, made use of the increased oxidation in the liver and testicle by injecting small doses of blood of the exophthalmic patient into a mouse.

The liver under these conditions becomes glycogen-free. From his experiments he concluded that the active agent circulating in the blood of the exophthalmic patient is far more active than any thyroxin preparation.

Mora[67] studied the shortening of the resorption time of intracutaneously injected salt solution in exophthalmic goiter, and Asher[68] made use of a similar dye test to demonstrate the central (sympathetic) effect on the thyroid gland.

The increase in permeability associated with increased metabolic activity should be followed by a negative calcium balance—and that it is, was recently demonstrated by Aub[69] and his associates, who also noted that osteoporosis may appear during the course of the disease.

Our observations indicate that the increased permeability determined by the blister is not necessarily related to the increased basal metabolic rate. In this respect, the results correspond with those noted in the markedly sympatheticotonic and nervous group in the members of which we observed an increased permeability without an increase in the basal rate. This fact, among others, inclines us to the view that we are dealing with two distinct factors—one, an underlying change in tissue reactivity, and another which is distinctly related to the calorigenic effect of the thyroid secretion. The question concerning the duality or multiplicty of the effect on the thyroid gland has repeatedly been raised; most recently by Csépai,[70] who, judging only by the effects on blood pressure, denies the probability.

The reactivity of the skin in patients with exophthalmic goiter presents a number of interesting features. The erythema after the applica-

66. Dresel, K.: Verhandl. f. inn. Med. u. Kinderh., Berlin, Jan. 7, 1929; abstr., Klin. Wchnschr. **8**:425, 1929.

67. Mora, J. M.: J. M. Sc. **177**:153, 1929.

68. Asher, L., and Pfluger, O.: Ztschr. f. Biol. **87**:115, 1927.

69. Aub, J. C.; Bauer, W.; Heath, C., and Ropes, M.: J. Clin. Investigation **7**:97, 1929.

70. Csépai, K., and Fernbach, J.: Arch. f .exper. Path. u. Pharmakol. **129**:256, 1928.

tion of ice appears rapidly, and the resistance of the skin to electric current is lowered, as Richter [71] has previously noted.

Lueg and Grassheim [72] studied the capacity of the skin for polarization in thyroid disease and noted that the increase in the basal metabolic rate usually parallels the increase in capacity for polarization. Curiously enough, the upper and lower portions of the body may show considerable difference. Nothhaas,[73] in examining the dermographic reaction, found a longer latent period in exophthalmic goiter.

Hoke [74] made use of a traumatic reaction (carbol-salt) and demonstrated an increased reaction of the skin in exophthalmic goiter and also after injections of thyroxin. Similar increases in reactivity were noted when milk or typhoid vaccine was injected.

In our preliminary discussion, we pointed out the occurrence of a dissociation of certain changes of the skin from the metabolic rate. We called attention to the fact that, following operation, the basal metabolic rate might return to normal but certain of the alterations of the skin become more pronounced. Such a dissociation of symptoms is, of course, a common observation in exophthalmic goiter and merely confirms our impression that the underlying change is dual. The treatment, too, would indicate this. Zondek [75] grouped the methods under three heads: (1) operative removal of the thyroid gland, (2) fixation of thyroxin in the thyroid gland (with iodine) and (3) treatment with certain of the narcotic drugs that change the surface of the cell.

König [76] added to this, thorough alkalinization, a procedure that might seem logical from the probable effect on the membrane of the cell.

THE NERVOUS PATIENT

It will be recalled that our nervous patients had a relatively low level of potassium with a practically normal level of calcium in the serum, were, in general, thin, usually showed an increased permeability of the capillaries, had a high resistance of the skin to electric current and a rather delayed reaction to ice.

Glaser [77] reported that there were observable differences in the amount of calcium in the serum in different psychic states in the same person.

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71. Richter, C. P.: Electrical Skin Resistance: Diurnal and Daily Variations in Psychopathic and Normal Persons, Arch. Neurol. & Psychiat **19**:488 (March) 1929.

72. Lueg, W., and Grassheim, K.: Ztschr. f. klin. Med. **110**:531, 1929; Klin. Wchnschr. **7**:647, 1928.

73. Nothhaas, R.: Klin. Wchnschr. **8**:820, 1929.

74. Hoke, E.: Wien. klin. Wchnschr. **33**:904, 1920.

75. Zondek, H.: Verhandl. f. inn. Med. u. Kinderh., Berlin, Jan. 7, 1929; abstr., Klin. Wchnschr. **8**:425, 1929.

76. König, W.: Klin. Wchnschr. **8**:634, 1929.

77. Glaser, F.: Med. Klin. **20**:1237, 1924.

Tomasson [78] published the most extensive work, studying the mineral metabolism of a large series of psychopathic patients. From his studies he concluded that the calcium fluctuations precede periods of mental instability and that they are inversely proportional to the mood of the patient. In the maniacal periods of maniac depressive insanity, the calcium in the serum is increased and he did not find any low values. Movement in itself is not responsible for this, although under hypnosis there is some lowering of the level. Alterations of the mineral equilibrium of the serum which Tomasson described would be indicative of a loss of calcium from tissues with a coincident penetration by potassium. With it, he found a slight alkalosis.

Hoff and Werner's [79] experiments indicate that in the neurotic patient one is dealing primarily with a lowering of the threshold between the vegetative and psychic centers, leading to obvious instabilities.

Kraus [80] definitely grouped "neurasthenia" as a vegetative disturbance, i. e., vagolability, electrolytic alterations not only being associated with the vegetative-neurotic stimulation but determining the type of the reaction.

Regarding the vegetative status as the fundamental background of all reactions, reproductive, developmental—irritability, in general—he conceived the neuroses as distinctly constitutional (as, clinically, they obviously are) with general psychic manifestations, or as organ neuroses with local vagotonic or sympatheticotonic overbalance. He assumed that it is potassium which plays the large rôle—nonionized potassium going over to ionized forms on stimulation; this would correspond with our observations. Insofar as the ultimate status of the individual (vital periodicity, reactivity) is, in its final analysis, the result of a balance between cosmic (external) and internal stimuli, we can understand that the constitutional status plus the conditioning effects influence the psychic reactions just as they would any other organ or tissue.

While there seems little doubt that we may legitimately associate changes in the permeability with functional changes in the nervous apparatus, the converse, that the nervous system may change the permeability of the capillaries is also probable; we may be dealing with a circular mechanism.

We have repeatedly stated that the stimulation of the sympathetic side of the autonomic nervous apparatus is associated with diminished

78. Tomasson, Helgi: Undersøgelser over nogle af blodets elektrolyter (Ca, K, Na, H) og det vegetative nervesystem saerlig hos patienter med maniodepressiv psykose, Copenhagen, Levín & Munksgaard, 1927.

79. Hoff, Hans, and Werner, Paul: Klin. Wchnschr. **7**:346, 1928.

80. Kraus, F.: Klin. Wchnschr. **6**:537, 1927.

capillary permeability. Vessels that have been deprived of their sympathetic innervation are more permeable.[81]

The work of Gellhorn,[64] definitely proving the increased permeability following pilocarpine and diminution following epinephrine, is in line with related demonstrations by many observers. We would, however, call attention to the fact that these effects are probably direct effects on the cell membranes. With thyroid and sex hormones increasing permeability (the observations of Asher, Gellhorn, Fröhlich and Zak[82] and others are convincing) and epinephrine and pituitrin diminishing permeability, and with a regulatory effect of the nervous system in controlling the output of the glands of internal secretion made probable, we can understand that an overflow of nervous impulses to such glands in certain persons would change tissue permeability. Asher and Pfluger[83] demonstrated increased activity of the thyroid gland under such conditions. This would in turn increase capillary permeability in general.

There is a close parallelism between "nervousness," capillary permeability, permeability of the meningeal barrier and the K/Ca ratio. In the menstrual cycle, the nervous manifestations are clinically obvious. The related blood chemistry has been well developed.[84] Heilig and Hoff[85] demonstrated the increased permeability of the meninges, and we have shown an increase in capillary permeability.[48] In our present series, the "nervous" persons have, in general, a distinct increase in permeability and with it, as a group, a low K/Ca ratio.

We have had the impression for a number of years that mental instability can result from changes in the ionic equilibrium and from changes in the capillary permeability, just as such alterations may change the reactivity of other tissues in the body. In a woman with a puerperal psychosis, for instance, we observed an unusually high capillary permeability.[86] In another instance, that of an individual in this series, we called attention to the fact that the patient's high capillary permeability occurred during a time of emotional stress incidental to stock market losses.

Perhaps no more striking association of mental disturbances with alteration of the vegetative system (particularly muscular abnormality) exists than in catatonia. Here we have definite evidence of the control

81. Yamamoto, J.: Biochem. Ztschr. **145**:201, 1924. Gabbe, E.: Ztschr. f. d. ges. exper. Med. **51**:728, 1926.

82. Fröhlich, A., and Zak, E.: Klin. Wchnschr. **8**:1540, 1929.

83. Asher, L., and Pfluger, O.: Ztschr. f. Biol. **87**:115, 1929.

84. Riddle, O.: Proc. Am. Philos. Soc. **66**:497, 1927.

85. Heilig, R., and Hoff, H.: Klin. Wchnschr. **3**:2049, 1924.

86. Petersen, W. F., and Lash, A. F.: Alterations in Permeability of Skin Capillaries During Pregnancy and Puerperium, Arch. Int. Med. **39**:12 (Jan.) 1927, table 3.

of the clinical picture through ionic alterations. Reese,[87] together with Loevenhart and Lorenz, demonstrated complete (though transient) restoration of catatonic patients to a normal condition when the latter were stimulated by means of carbon dioxide respiration. Gordonoff and Walther [88] also showed a marked increase in potassium in the blood and blood corpuscles of such patients.

GLAUCOMA

Our examinations indicate that the patient with glaucoma has a lability of the cardiovascular renal system. This seems in accord with the observations of other investigators. Sulzer's [89] observations led him to believe that primary glaucoma is due to a vascular disturbance. Schmidt [90] noted that the water balance of the body is atypical in glaucoma. Thus, in the normal person, the ingestion of water is not followed by a change in eye pressure; in the glaucomatous patient, the pressure is increased. While Schmidt does not believe that the effect is wholly osmotic, he does insist that it concerns a capillary change.

One must, of course, not forget that local anatomic changes—size of the lens, dilatation of the pupil, etc.—are probably the determining factors; the initiation of the disturbance may, however, be closely related to sudden changes in capillary permeability. Goldenburg [91] recently discussed this subject in some detail.

TUBERCULOSIS

Constitution.—The human body reacts fundamentally in two different ways to tuberculous infection: one resulting in a relatively benign process, developing slowly, becoming quiescent through cicatrization and proliferative; the other resulting in an exudative process with fluid effusion, relatively rapid progression and dissolution of tissues. Clinically, we meet every phase of resistance fluctuating between these two extremes, extremes which must depend on differences in irritability of the tissues. The greater the irritability the more marked is the response, the greater the tendency to an exudative process. The less the irritability the greater is the tendency to cicatrization.

With these premises granted, the problem obviously involves the autonomic status of the organism as a whole, the status of the various organs and the question of variations in the vegetative status as modified by the infection.

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87. Personal communication to the authors.
88. Gordonoff, T., and Walther, F.: Klin. Wchnschr. **8**:1179, 1929.
89. Sulzer, F.: München. med. Wchnschr. **75**:768, 1928.
90. Schmidt, K.: Med. Klin. **24**:859, 1928.
91. Goldenburg, M.: Illinois M. J. **52**:474, 1927; Am. J. Ophth. **11**:290, 1928.

It also must be kept in mind that even the acutely exudative process may result in utter destruction, i. e., digestion and removal of the virus and the inflammatory exudate. This latter method is probably a common method of disposal of the smaller lesions, much more common, than mere clinical observation would lead one to suspect.

Of course, the relation of "constitution" to tuberculosis is involved in this problem and is one that has interested physicians since time immemorial. The difficulty has been the definition of the term "constitution." In this way the "asthenic," "phthisical," "respiratory" type of the French has always been stamped as that of the potentially tuberculous person.

Borchardt [92] discussed the reactivity of the tissues to tuberculous infection in relation to constitutional types. In the "Status-Irritabilis" of Wunderlich, he found more localization in the mucous membranes, the skin, the serous membranes, etc., with a relatively good prognosis and good connective tissue reactions. In the "asthenic" type (Stiller) or the lymphatic arthritic type (Pfaundler) there is apparently a lessened reaction. We are dubious concerning the value of such classifications of constitution for the reason that in the adult the genotype must be greatly modified by the conditioning factors. One of the most important of these we consider to be the probability of a relatively long established preexisting tuberculous infection dating, not infrequently, from childhood. The tuberculous adult who is finally classified as of the "asthenic" or "phthisical" type must frequently be what he is—physically, physiologically and psychically—because of this infection.

While one ordinarily thinks of constitution in its more tangible form, one forgets the possible constitutional differences in the organ reactions and tissue reactions. Thus a congenital deficiency may indeed be expressed anatomically in the structure of the elastic tissue of an organ or in a certain degree of infantilism or in the more rapid senescence that one sees commonly in the teeth or the hair or the structures of the eye in certain families.

The Autonomic Status.—Considerable literature has developed that deals with the autonomic nervous system and tuberculous infection. In this country, Pottenger [93] has for many years pioneered in studying symptomatology with particular relation to the underlying autonomic alteration. There is no uncertainty concerning this phase of the problem nor is there any question concerning the general autonomic instability as expressed in the reactions of the vasomotor, the gastro-intestinal and the mental apparatus. Redeker [94] has but recently reemphasized the

92. Borchardt: Deutsche med. Wchnschr. **47**:1159, 1921.

93. Pottenger, F. M.: Symptoms of Visceral Disease, St. Louis, C. V. Mosby Company, 1929.

94. Redeker, F.: Beitr. z. Klin. Tuberk. **70**:259, 1928.

general psychic instability as part of the reaction of the tissues to the invading organism. A most interesting histologic confirmation has come from Michejew and Pawljutschenke,[95] whose conclusions we shall quote at some length:

> The patho-physiological explanation of the clinical findings in tuberculosis is often most conflicting, due we believe, to incomplete methods of examination. There is no doubt, however, that the tuberculous processes bring about changes in the functions of all organs, not only directly, but indirectly, through pathological alterations of the vegetative endocrine correlations. The entire "vegetative system" in the sense of Zondek-Kraus is destroyed. . . .
>
> Our examinations show that the tuberculous processes bring about diffuse changes in the vegetative centers. It is therefore impossible to associate definite vegetative findings with strictly limited anatomical lesions. We assume furthermore that in the central nervous system, no fixed centers for every type of metabolic activity exist, but that we deal rather with the projection of certain physico-chemical processes on certain nuclei. The diffuse character of the lesions found by us lead us to suspect that in tuberculosis, certain alterations exist that accelerate the penetration of the toxin into the central nervous system.
>
> Leaving aside the factor of predisposition or constitution, we should like to point out that one of the chief factors must be this increase in permeability of the "hematoencephalitic" or "capillary" barrier which makes possible this effect of toxin on the central nervous system. It is not necessary to dwell on the change in the concentration in calcium as one of the factors involved in this alteration.
>
> The complexity of the balance between the individual vegetative system and the infection accounts for the multiplicity of symptoms and the variety of symptom complexes in tuberculosis.
>
> It seems probable that the early change in the permeability of the "barrier" plays a rôle in the early appearance of certain nervous manifestations which we may regard as pre-tuberculous.

Changes in general cellular permeability apparently alter chronaxia, for Förster[21] has shown that it is lowered by epinephrine, calcium chloride and parathyroid, and increased with hydrochloric acid, philocarpine, choline, thyroxin, etc., and Förster ascribed periodic fluctuations in sensitivity to impulses to alterations in chronaxia brought about by general changes in the permeability. Lapicque and his co-workers[96] had previously demonstrated this phenomenon. Both peripheral and cerebral changes in permeability apparently directly influence the nervous response, and the dependence of the effect of the impulses on the state of the organ has been discussed previously at length.

With the recognition that the local autonomic status of the tissues is of importance in the resistance to tuberculosis, the study of that status has concerned a number of workers.

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95. Michejew, W. W., and Pawljutschenke, E. M.: Arch. f. Psychiat. **84**:227, 1928.

96. Lapicque, M.: Soc. de biol. Paris **74**:32, 1913. Obre', A.: ibid. **88**:585 1923. Florkin, M.: ibid. **97**:1804, 1927.

Eppinger and Hess [97] were the first to point out that the majority of tuberculous patients give a "vagotonic" reaction to epinephrine. Deutsch and Hoffman [98] reported that the patient with early tuberculosis gives a "sympatheticotonic" reaction to epinephrine. Later, the reaction is more irregular, with "vagotonia" preponderating. Dresel [99] confirmed this observation.

A most extensive series of observations was reported by Guth,[100] whose interpretation, in general, follows the line of Danielopolu. He noted that tuberculotoxin acts amphotropically, first irritating both components, later leading to a depression, with emphasis on the vagus side. In general, most of the exudative patients were found to be "vagotonic"; most of the productive types, "sympatheticotonic."

Glaser's study,[77] as well as Kading's [101] work, indicates that the chronic tuberculous person is "sympatheticotonic." Pende [10] came to the conclusion that if the tuberculous person is first "sympatheticotonic" and then becomes "vagotonic," the prognosis is poor, whereas if the tuberculous person is primarily "vagotonic," the process is usually relatively benign. Géza,[102] on the other hand, found "vagotonia" occasionally present with some productive forms.

Kamsler [103] studied the vascular response to epinephrine, atropine and neucesol in a group of tuberculous patients. He was careful to make the tests only in men and at the same time of the day. He found no apparent relationship between the vegetative response and the prognosis, but noted that the pyknic types responded with low blood pressure curves.

Interesting is his agreement that the vegetative response to these various pharmacologic agents is merely one of an accentuation of a preexisting orientation and that it is dependent particularly on calcium concentration. He insisted that one should speak merely of an irritability or a depression of the vegetative system, as did Bovet.[104]

The autonomic status as judged on the basis of the blood pressure response to epinephrine in our series indicates a decided lessening of the reactivity of the tuberculous group as contrasted with the group of 100 normal persons. So, too, of the twenty-four patients who died, those who lived the longest had the more marked "sympatheticotonic"

97. Eppinger, H., and Hess, L.: Die Vagotonie, Berlin, 1910.

98. Deutsch, F., and Hoffman, O.: Wien. klin. Wchnschr. **26**:569, 1910.

99. Dresel, K.: Ztschr. f. klin. Med. **101**:70, 1924.

100. Guth, E.: Beitr. z. Klin. d. Tuberk. **53**:94, 1922; **54**:186, 1923; **55**:33, 1923; **60**:39, 1924. Glaser, W.: Ibid. **55**:390, 1923.

101. Kading, K.: München. med. Wchnschr. **71**:225, 1924.

102. Géza, Gali: Gyógyászat **62**:232, 1922; abstr. Zentralbl. f. d. ges. Tuberc. Forschung **19**:31, 1923; **22**:493, 1924.

103. Kamsler, A.: Klin. Wchnschr. **7**:110, 1928.

104. Bovet, A.: Schweiz. med. Wchnschr. **58**:483, 1928.

reactions to tuberculin when they were examined, and of the four patients who were losing weight at the time of examination but subsequently improved, three showed a "sympatheticotonic" reaction.

We have repeatedly expressed our reservation concerning the use of the terms "sympatheticotonic" and "vagotonic." We should much prefer to discard them entirely, resolving the term into the various components, i. e., the local status of the tissues, whether active or resting, whether with increased or diminished permeability, whether with dilatation or constriction of the vessels, whether with relative alkalosis or relative acidosis, etc. The terms "sympatheticotonic" and "vagotonic" are altogether too conflicting and too broad to be useful.

We shall examine the local reaction from this point of view. About a tuberculous focus there exists a zone of tissue stimulation (irritation) which may range from slight and transient effects that are promptly reversed by the more remote cells of the focus, through all the stages of fatigue and finally to death. In the stage of stimulation, the metabolic rate, acidity, permeability, cellular exchange and enzymatic (digestive) processes, are all increased; calcium leaves the tissue and sodium and potassium enter. A general lessening of tissue cohesion takes place. In general terms, we can regard this as an abnormal status of the vegetative balance in which the autonomic nervous system, the ionic equilibrium, the hormones and the tissue metabolites play their rôles.

Tissue changes associated with autonomic derangement are usually associated with local injury, more rarely with changes in the entire organ and sometimes with alterations in the vegetative balance involving the entire body.

1. Alterations in the nervous component of the vegetative system may originate from (*a*) purely psychic effects, (*b*) direct injury of nerves, as for instance, the pressure of enlarged mediastinal glands on the vagus, and (*c*) central (midbrain) injury, illustrated strikingly in some cases of postencephalitic parkinsonism and in some of the intoxications that follow bacterial or other poisoning.

2. Endocrine dysfunction plays a rôle. Diminution of the suprarenal secretion and perhaps of the pancreatic hormone would have a tendency to increase permeability, as would hyperfunction of the sex glands and of the thyroid gland. The activity is, however, conditioned to a large extent by the ion equilibrium existing at the cell surface, i. e., by the preexisting state of activity of the cell.

3. Tissue reaction is also involved. Increased acidity increases permeability, and this goes hand in hand with a release of calcium from the cells.

The Vascular Reaction to Tuberculin.—Given this background, let us examine the status of the tuberculous tissue and the tuberculous

person as a whole. We know, in general, that the reaction of the tuberculous tissue, as recently shown by Schade and Claussen,[105] is on the acid side (from p_H 7 to p_H 7.3) and exactly at the optimum for growth of the tubercle bacillus. We know, too, that the peripheral dilatation of blood vessels depends not on central vasomotor regulation, but on the peripheral effects of dissimilation, including primarily, increased acidity, as well as the effects of histamine and acetylcholin.

Fleisch recently added a demonstration which is most convincing.[106] Tuberculin itself always causes vessels to dilate.

In preceding discussions, we have pointed out that stimulation of smooth muscle (in the metabolic and membrane sense) is associated with relaxation, i. e., lengthening of the cell. The reason for this seemingly paradoxic point of view we need not again elucidate; the physiologic observations have been generally accepted. When we extend this to the smooth muscle of the blood vessel wall, direct stimulation of cells must result in the dilatation of the vessel. Epinephrine, which makes the membrane less permeable, apparently causes contraction, irrespective of its presumable effect via the sympathetic mechanism.

Tuberculin stimulates the normal organism;[107] in the tuberculous animal, the stimulation may proceed to fatigue. We should expect that in the isolated vessel preparation perfusion with tuberculin would cause dilatation. Experiments of Preobraschewsky[108] are now available on this point. He found that tuberculin causes the normal vessels to dilate, with contraction following. In the tuberculous animal, the preliminary dilatation persists indefinitely. Buillion acts like tuberculin.

He also observed that a vessel preparation of animals with advanced tuberculosis showed a lessened reactivity to epinephrine. We believe this to be explained on the basis of the well known observation that epinephrine causes little or no contraction of vessels in irritated (inflammatory) regions. When tuberculin was injected into animals and vessel preparations were then perfused, the reaction to tuberculin (and buillion) was irregular. Similar experiments were made by Friedberger and Seidenberg.[109]

Here a physiologic preparation offers the counterpart of the intravital phenomena that take place when tuberculin is injected or that must obtain when tuberculin is released from a focus. The vessels are

105. Schade, H., and Claussen, F.: Beitr. z. Klin. d. Tuberk. **62**:300, 1925.

106. Fleisch, A.: Klin. Wchnschr. **8**:1315, 1929.

107. Levinson, S. A., and Petersen, W. F.: Am. Rev. Tuberc. **15**:681, 1927.

108. Preobraschewsky, A. M.: Ztschr. f. Immunitätsforsch. u. exper. Therap. **63**:132 and 139, 1929.

109. Friedberger, E., and Seidenberg: Ztschr. f. Immunitätsforsch. u. exper. Therap. **51**:276, 1927.

directly stimulated. In place of a normal reversal occurring, the tissue is readily fatigued and reversal is delayed, i. e., dilatation persists.

Therapeutic agents that have been useful in tuberculosis are those most frequently directly active on the capillaries, and even that most specific agent, tuberculin, is effective in the therapy of tuberculosis probably not because of its immunologic properties but because of its influence on the caliber of the arterioles and the permeability of the capillaries (and tuberculous lesions), as originally supposed by Moro.

It is the vascular reaction that must always be regarded as the basis of any understanding of the tuberculous lesion. Physiologic vascular processes, which can be interpreted on the basis of stimulation, of rest or of fatigue, have been disguised by obtuse and conflicting immunologic concepts. We have come to consider resistance without reference to specific concepts, and Kalbfleisch [110] seems to have reached the same position when he stated that there is no room for the term "immunity" in the pathology of tuberculosis. This is quite apart from the persistent attack on the specificity of the tuberculin reaction.[111] We have felt justified in concluding from our experiments [112] that the reaction of the normal animal differs from that of the tuberculous animal only in degree. Kalbfleisch's conclusions in this connection are as follows:

> There is only one thing that differentiates the effect of tubercle bacilli in tuberculous animals from the effect in the healthy animal; these are differences in the reaction of the vascular system, which, depending on susceptibility to the irritation and reactivity of the nervous elements of the vascular bed of the tuberculous animal, bring about quantitative differences from the reaction of the normal animal, and thereby bring about quantitatively altered effects in the cells and fibers of the tissue.

All the therapeutic agents of the "reactive" class, tuberculin, sodium aurothiosulphate, hetol, etc., act seemingly in a relatively simple way.[113] They first make the tissues more permeable, and later the tissues become less permeable for a considerable period of time.

The focal reaction, whether in the form that is obvious clinically or consisting merely of the imperceptible biologic actions following the injections of minute doses of the agents in question, is a reaction that depends on changes in permeability of the capillaries about the tuberculous focus.

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110. Kalbfleisch, H. H.: Beitr. z. Klin. Tuberk. **70**:465, 1928.

111. Selter, H., and Bloomenberg, W.: Beitr. z. Klin. d. Tuberk. **66**:105, 1927. Beiling, R., and Keller, W.: ibid. **69**:577, 1928. Keller, W., and Dölter: ibid. **60**:444, 1928.

112. Petersen, W. F.; Jaffe, R. H.; Levinson, S. A., and Hughes, T. P.: J. Immunol. **8**:387, 1923. Petersen, W. F., and Levinson, S. A.: Am. Rev. Tuberc. **8**:122, 1923.

113. Levinson, S. A.; Petersen, W. F., and Milles, G.: Am. Rev. Tuberc. **16**:285, 1927.

Biologic processes, such as the menstrual cycle, the effects of season, etc., that are associated with an increase in capillary permeability and autonomic imbalance are apt to be associated with clinical activation.

A most enlightening condition concerns the relation of the mortality from tuberculosis to the season. The association of clinical activity with the spring goes back to Hippocrates. A recent statistical correlation is that of Herrup from the Faroe Islands.[114] The change in the K/Ca ratio and the seasonal changes in the size and activity of the organs made apparent in the work of Riddle[115] and Brown[9] bring us nearer a logical explanation of the clinical observations.

Clinically advancing tuberculosis is associated with increased capillary permeability; healed tuberculosis with diminished permeability. It might seem warranted to draw the conclusion that increase in capillary permeability, however produced, would unfavorably influence a tuberculous lesion, and that, conversely, diminished permeability must be associated with improvement.

We shall not endeavor to include in this summary a review of all the results of the examinations made, but shall discuss briefly only the more important phases of the work.

Correlations Based on Clinical Classifications, Weight Curve, Clinical Prognosis and Fatalities.—The Clinical Classifications of the National Tuberculosis Association (table 2, part VIII A, p. 168): Apart from the obvious correlations (tuberculosis fixation, Darányi reaction, basal metabolic rate, pulse rate, etc.), there are no consistent changes as we proceed from the incipient A to the far advanced C cases. We might anticipate this. The incipient A group will include patients in whom the disease may develop rapidly, may heal or may become chronic. The far advanced C group will include patients who have had chronic tuberculosis for years, with relatively high resistance. In addition, there will be many persons with febrile tuberculosis, with peripheral vasoconstriction, made evident in the prolongation of the blister time.

Weight Curve (table 3, part VIII A, p. 168): The grouping of patients by relative increase or decrease of weight at the time of examination begins to offer something more tangible. It is to be noted that the persons with healed tuberculosis (roentgen shadows only) have a permeability of 65. Persons with roentgen evidence of active tuberculosis (very chronic) have a permeability of 59. Our sanitarium group shows a progressive increase to 69.6. There is, however, no consistent relation to the blood chemistry, but the blood proteins increase, and the McClure-Aldrich test is markedly shortened.

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114. Herrup: Beitr. z. Klin. d. Tuberk. **68**:739, 1928.

115. Riddle, O.: Am. Naturalist **61**:481, 1929.

Prognosis (table 9, part VIII A, p. 176): Here we begin to obtain interesting clinical and laboratory correlations. The relation to permeability and to calcium has been discussed. We note that the "vagotonic" reaction to epinephrine increases; the epinephrine flare becomes smaller while the thyroxin flare becomes larger, the cholesterol/lecithin ratio becomes smaller, the McClure-Aldrich test becomes shorter and the tuberculin reaction smaller.

Fatalities (table 10, part VIII A, p. 181): When, finally, we consider the patients who died and place them in two groups (those that lived an average of forty-five months after the onset of clinical activity and those that lived an average of sixty-five months), we find that the less resistant group had a high capillary permeability, much less calcium, less cholesterol, a higher globulin content and a shorter McClure-Aldrich time, while there were more "sympatheticotonic" persons in the group that lived longest.

Calcium.—We must regard the calcium metabolism as in some way closely associated with the clinical condition of the patient. In the group with low calcium, for instance, we find more deaths. We find that the persons with healed tuberculosis have higher calcium (10.3), that persons with good prognosis have higher calcium (10.7 and 10.6), that those with stationary disease have lower calcium (9.1); as we then turn to those with poor prognosis, the calcium level again rises (10.2), owing, we believe, to the probability that with a negative balance, calcium is being mobilized from the tissues. We have previously discussed some of the literature dealing with calcium in tuberculosis (part III).

More and more clinical evidence is accumulating which indicates the importance of calcium in tuberculosis in regard to both the reactivity of the tissue and its influence on the disease process. Sternberg [116] found lower serum calcium in the most advanced cases; Schaefer,[117] an increase in the calcium in the lung in chronic tuberculosis. Sweany [118] and his associates found the calcium levels about normal, and Hoyle,[119] admitting the clinical impression of improvement with calcium, regarded the experimental evidence as still lacking. He found an early increase in calcium in rabbits infected with tuberculosis, with a terminal decline. The lack of experimental confirmation is, however, not necessarily a criterion of clinical value, for the reason that tuberculosis in the guinea-pig and in the rabbit, particularly, is decidedly different from tuberculosis in man. As a matter of fact, Henner [120] observed that when

116. Sternberg, T.: Beitr. z. Klin. d. Tuberk. **71**:737, 1927.

117. Schaefer, R.: Beitr. z. Klin. d. Tuberk. **69**:86, 1928.

118. Sweany, H. S.; Wethers, A. T., and McCluskey, K. L.: Am. Rev. Tuberc. **8**:405, 1924.

119. Hoyle, J. C.: Quart. J. Med. **22**:451, 1929; J. Pharmakol. & Exper. Therap. **34**:317, 1928.

120. Henner: Beitr. z. Klin. d. Tuberk. **51**:56, 1929.

calcium dust (Ca [OH2]) was used, tuberculous animals not only showed less involvement than animals exposed to other dust, but actually less than the control animals not exposed to dust. The clinical literature, as mentioned previously, is rather conflicting, and various methods have been suggested for the administration of calcium, as well as various indications. Thus Siegel [121] stated that he obtained improvement in 50 per cent of his cases with calcium inhalation. Becker [122] treated 150 patients with intravenous medications and mentioned improvements, particularly in bilateral involvements.

Cholesterol.—That cholesterol usually diminishes with progressive tuberculosis has been frequently noted. This, of course, is in line with the change in cholesterol metabolism apparent in other infections.[123] In recent work, Shope [124] brought experimental evidence that increasing serum cholesterol probably plays some rôle in prolonging the life of experimentally infected guinea-pigs, confirming clinical observations that date back a number of years.[125] Borchardt,[126] as well as Leupold and Bogendörfer, recently presented further experimental evidence concerning the usefulness of cholesterol in increasing resistance to infection, an increase which seems to follow specific immunization, too.[127] The association of a low cholesterol in tuberculosis with poor prognosis was noted by Rieter,[128] and is in line with the results of our observations.

It is rather interesting to note that Glaser [129] published clinical observations indicating that the cholesterol level of the blood may change with changes in the psychic state just as does the calcium level, while Wade [130] found an increase in cholesterol associated with a decrease in the serum calcium.

Reactivity of the Skin.—The reactivity of the skin of the tuberculous patient has been a subject of study for so many years by so many investigators that we shall make no effort to review the literature, but merely point out that there is a general recognition of the fact that, apart from the so-called "specific" factor, the degree of reactivity is dependent on the status of the skin, i. e., that the systemic factors play a decided rôle. Thus, the reactivity to tuberculin diminishes in the

121. Siegel, H.: Ztschr. f. Tuberc. **53**:256, 1929.

122. Becker, A.: Ztschr. f. Tuberc. **53**:198, 1929.

123. Heening, B. H.: J. Biol. Chem. **53**:167, 1922. Gabrila, J., and Vior, V.: Arch. d. mal. de l'app. digestif **18**:601, 1928. Heinze, V.: Ztschr. f. Tuberc. **52**:199, 1928.

124. Shope, R.: J. Exper. Med. **48**:321, 1928.

125. Valois, G.: De la cholesterinenne an cours de la tuberculose pulmonaire, Lyon and Paris, A. Maloine et fils, 1912. Farini, A.: Gazz. d. osp. **35**:993, 1914.

126. Borchardt, W.: Klin. Wchnschr. **8**:1179, 1929.

127. Barbara, M.: Arch. di pat. e clin. med. **8**:379, 1929.

128. Rieter, H.: Klin. Wchnschr. **8**:1158, 1929.

129. Glaser: Klin. Wchnschr. **6**:2377, 1927.

130. Wade, P. A.: Am. J. M. Sc. **177**:790, 1929.

terminal stages in tuberculosis, during intercurrent disease and with "desensitization" due either to tuberculin therapy or as a result of non-specific injections.

Nor is it possible to review the extensive literature concerning reactivity of the skin, in general. The monographs of Lewis,[131] the shorter works of Hecht,[132] Pulay[133] and Luithlen,[134] the reviews of von Groer[46] and Ebbecke[135] are available for this purpose.

We would, however, refer again to the work of Kauffmann.[52] Kauffmann observed that when he placed cantharides on the skin of a patient with pneumonia, several distinct stages of reactivity could be distinguished. First, during the febrile period, he observed a delayed or absent reaction. Second, with defervescence a marked reaction; third, after defervescence, a period of transition during the next ten days to a maximum monocytic reaction in the exudate; fourth, for a varying interval, another period of inhibition or delayed reactivity (adaphorea of von Groer, presumably not the same as local immunity in the specific sense).

As cantharides constitute a chemical irritant acting primarily on the cell membranes, specific sensitization plays no rôle, but the results are nevertheless of interest for the tuberculin reaction. Let us examine the possible correlation.

1. During the febrile stage there exists a peripheral inhibition (vasoconstriction). Cantharides can act on the cells, but little or no exudate forms. The direct injury to the cells is great because there is no dilution, and healing takes place slowly (see discussion of herpes). Applied to tuberculosis and the tuberculin reaction, it means that during the febrile stage of an intercurrent disease, the tuberculin reaction is inhibited because of the change in the status of the skin; during the terminal stages of tuberculosis itself, this factor is also operative.

2. During the period corresponding to defervescence in pneumonia when, as Meyer pointed out, vascular dilatation is accentuated, this peripheral factor is negated, and vigorous reaction takes place. Applied to the tuberculin reaction, this corresponds to the period of maximum response when sensitization (i. e., direct cellular response and vasodilatation due to the direct effect of the tuberculin) prevails at a time during which peripheral vasodilatation is compensating for the increased metabolism going on in the body, i. e., during the period of vasomotor

131. Lewis, T.: The Blood Vessels of the Human Skin, London, Shaw & Sons, 1927.

132. Hecht, A. F.: Ztschr. f. d. Ges. exper. Med. **33**:23, 1923.

133. Pulay, E.: Stoffwechsel und Haut, Vienna, Urban & Swartzenberg, 1923.

134. Luithlen: Pharmakologie der Haut, Berlin, Julius Springer, 1921.

135. Ebbecke, U.: Deutsche med. Wchnschr. **50**:1, 1924; Naturwissenschaften **14**:1131, 1926.

instability, when the tuberculotoxin has not yet stimulated the liver to the degree that the splanchoperipheral balance has become fixed. The autonomic skin function is, in other words, practically normal insofar as lability is concerned.

3. Finally, in the pneumonia patient, at varying intervals after the crisis (from three to five weeks), a period supervenes during which the skin is again nonreactive. Here we are not dealing with a peripheral vasoconstriction present during the acute febrile stage. The tissue cells have changed. The cell membranes are no longer irritated to the same degree by the same amount of the irritant. The cell membranes have become less permeable. Applied to tuberculosis we find the same picture during periods of relative quiescence of the lesions, with recovery; after a course of tuberculin treatment, or after a series of relatively bland nonspecific injections.

These are wholly nonspecific effects which influence the reactivity of the skin in general, but they are of importance for the problem of tuberculosis because the vegetative status of the skin and the vasomotor activity are underlying factors that determine the type of reaction to all toxic agents.[136]

That these different states of reactivity of the skin are associated with differences in the underlying physicochemical equilibrium we need not again emphasize. However, the experiments of Klauder and Brown,[137] which are pertinent, must be mentioned. In their experiments, a correlation of the blood and skin chemistry with the intensity of the skin reaction is made evident.

Apparently, differences exist that depend on the type of irritant; for instance, calcium seems to be much more closely related to the effect of epinephrine and to the blister time; potassium, to the effect on the skin of thyroxin and caffein. Needless to say, there are many other modifying factors (table 1, part I).

Leukocytic Reaction.—Among the reactions that we have followed with particular interest has been the effect of the intracutaneous injection of a bland protein on the leukocytic curve.

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136. Roeckemann: Beitr. z. Klin. d. Tuberk. **49**:301, 1922. Stutz: Schweiz. med. Wchnschr. **54**:676, 1924. Schuberth, A.: Beitr. z. Klin. d. Tuberk. **69**: 273, 1928.

137. Klauder, J. V., and Brown, H.: Experimental Studies in Eczema: I. A Study of the Sensitivity of the Skin of Rabbits to Chemical Irritants Under Experimentally Induced Conditions, Arch. Dermat. & Syph. **11**:283 (March) 1925; II. A Correlation of the Chemistry with the Irritability of the Skin of Animals Under Normal and Under Experimentally Induced Conditions, ibid. **15**:1 (Jan.) 1927; III. The Rôle of Sympathetic Nervous Irritability in the Rabbit, ibid. **19**:52 (Jan.) 1929; IV. The Correlation of the Potassium-Calcium Ratio in the Serum and in the Skin of Rabbits with the Irritability of the Skin, ibid. **20**: 326 (Sept.) 1929.

Intracutaneous injections bring about systemic effects, not only through the agency of the injected solution, but through the stimulation of the skin. Perhaps this stimulation of the skin is associated with liberation of histamine; perhaps it is due to a purely autonomic upset of the type that we have illustrated in charts 2, 3 and 4. Lewis reported experiments in which multiple areas of irritation of the skin resulted in a distinct systemic effect due, according to his hypothesis, to the actual liberation of enough histamine to bring about a general reaction.

Our composite curves indicate that when patients are classified on the basis of increasing, stationary or decreasing weight, the leukocytic reaction in the losing group is that of a rather marked primary leukopenia following the intracutaneous injection. Such a group of patients shows a coincident lowering of the blood pressure. We ascribe this to the fact that in this group the splanchnic vascular bed is more easily thrown out of balance with consequent accentuation of splanchnic stimulation and dilatation and a resulting accumulation of leukocytes in the splanchic area. The reactions merely afford additional evidence for the supposition of an altered vegetative status with progression of the disease.

Therapeutic Considerations.—Granted that the tuberculous lesion can be made clinically innocuous in one of two ways—(1) by digestion and (2) by complete encapsulation—the former method would be supported therapeutically by any measures that increase vascularization, increase enzymatic processes, increase permeability or, in general terms, bring about tissue stimulation, with relative acidosis, or the so-called "parasympathetic status."[138] The inherent danger lies (1) in the possibility of dissemination of the virus, (2) in the diffusion of toxic products and (3) in the possibility that stimulation may proceed to fatigue and death. We can readily understand that only sluggish lesions of the peripheral type or small lesions in the more vascular organs can be so treated with any degree of safety.

The second method, complete encapsulation, would be supported therapeutically by methods that decrease vascularization, decrease enzymatic processes, decrease capillary permeability or, in general terms, bring about rest of tissue or a "sympathetic" status,[139] with relative alkalosis. Here one must assume a therapeutic indication in the more extensive lesions, especially of the vascular organs.[140]

From the point of view of constitutional types, we can see that our heavy type should offer a general biologic status of diminished permea-

138. To be differentiated from vagotonia (see page 296).

139. To be differentiated from sympatheticotonia (see page 296).

140. The vascular endothelium of the viscera—liver, kidney, spleen, gastrointestinal tract—is normally more permeable than that of the peripheral tissues.

bility, lower metabolic rate and more sluggish inflammatory reactions that would seem favorable for the development of a slowly progressive, relatively benignant lesion. Presumably, in endocrine balances we would see less effect of the thyroid gland, with probably more effect of the pituitary gland, and in some cases more secretion of epinephrine.

Our slender type should offer two possibilities: a person, who, because of intense reactivity—with relative acidosis, increased metabolic rate, increased permeability, etc.—might, under certain circumstances, succumb to the infection rapidly, especially if infected with a large dose of the virus; and another person of the same type who might readily and rapidly dispose of tubercles, with relative freedom from clinical symptoms. The latter would presumably have more thyroid secretion, more sex gland secretion and varying degrees of suprarenal and pituitary activity.

It is perfectly obvious to us that in the intricate biologic picture of inflammation presented by tuberculosis innumerable possibilities exist. We have merely delineated the extremes. We would, however, reiterate that in clinical tuberculosis, it is the vascular mechanism that must always be in the foreground of consideration.

The particular therapeutic studies that have been introduced in the final paper of the tuberculosis series (VIII C, p. 236) are to serve only to illustrate several points in connection with the theoretical deductions; they are not to be regarded as clinical evidence for another cure for tuberculosis. They indicate that:

1. Pilocarpine (case of sister A, part VIII C, p. 241), which makes the capillaries more permeable, may be followed by dissemination.

2. Epinephrine (case of sister B) which normally is not only diphasic but amphotropic, may, when it makes capillaries less permeable, diminish clinical activity; or may make the capillaries more permeable and increase clinical activity (case 2, under "Reports of Other Cases," part VIII C, p. 249).

3. Pituitrin, which apparently acts more specifically on the cell membrane in lessening permeability (even in irritated tissues) may lessen clinical activity (cases 4 and 5).

4. Alkalosis is apparently useful (case 1) and stimulation of the skin by means of a skin burn, which theoretically should result in a peripheral dilatation and a splanchnic constriction, may also be useful (case 3).

With investigators in tuberculosis becoming more and more interested in tissue activity as a factor in resistance, many therapeutic procedures will be offered and exploited. The Gerson diet has already been capitalized. Here a diet predominantly of vegetables and fruits with its tendency toward alkalinization is advised with a salt-free oat-

meal diet, with its contrary tendency, and a proprietary salt mixture is added for good measure. Of course, the clinical reports are conflicting. If the Gerson diet really tends to bring about tissue acidosis, it should be useful in the sluggish peripheral types of infection, and actually the results in infection of the skin seem to be encouraging. On the other hand, there appears to be little consistent effect in the pulmonary lesions. As is the case with so many cure-alls the proponents here forget the innumerable individual features of each clinical picture and that a therapy which may be admirable for a sluggish tuberculosis of the skin is by no means necessarily useful for a visceral tuberculosis.

Practically every "cure" has met with this fate, and it must be the fate of every type of treatment that depends on tissue reactivity for its curative properties. "Stimulating" substances—tuberculin, hetol and sodium aurothiosulphate, for example—are active in sufficiently large doses by increasing permeability. And with large doses, injury almost invariably results. In small doses, they are sometimes useful because the transient stimulation and increased permeability are followed by a reversal—with a persisting impermeability. The agents that might presumably act in a contrary direction, epinephrine as originally suggested by Sargent, or calcium, may be useful when the preexisting state of the tissue is favorable. If not, one may get "paradoxic" effects with increased permeability and clinical injury. Even the physical agents, particularly heliotherapy, are followed by identical results. Sunlight may activate lesions in certain persons and may be useful in others.

We have the conviction that if we once begin to plan the therapeutic attack in tuberculosis less from the point of view of the immunologists and pharmacologists and more from that of the inflammatory reaction and its physiologic and physiochemical aspects, we shall be able to devise a more rational therapy.

What has been detailed for a chronic infection like tuberculosis has been presented merely to illustrate a point of view which we believe may be useful in other therapeutic problems.

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